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**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 12 January 1999 (12.01.99)	
<b>International application No.</b> PCT/US98/10566	<b>Applicant's or agent's file reference</b> BMSQ012P
<b>International filing date (day/month/year)</b> 20 March 1998 (20.03.98)	<b>Priority date (day/month/year)</b> 27 March 1997 (27.03.97)
<b>Applicant</b> SCHADE, Deborah, A. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
14 October 1998 (14.10.98)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Ting Zhao  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>BMSQ012P</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 98/ 10566</b>	International filing date (day/month/year) <b>20/05/1998</b>	(Earliest) Priority Date (day/month/year) <b>27/03/1997</b>
Applicant <b>BRISTOL-MYERS SQUIBB COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant

☒ the text has been established by this Authority to read as follows:

**USE OF DOCOSAHEXANOIC ACID AND ARACHIDONIC ACID ENHANCING THE GROWTH OF PRETERM INFANTS**

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

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## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MJ-729/PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/10566	International filing date (day/month/year) 20 MARCH 1998	Priority date (day/month/year) 27 MARCH 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 31/20 and US Cl.: 514/560, 558		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

## 3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14 OCTOBER 1998	Date of completion of this report 15 OCTOBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer DWAYNE C. JONES
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/10566

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☒ the international application as originally filed.

☒ the description, pages 1-80, as originally filed.

pages NONE, filed with the demand.

pages NONE, filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. 1-13, as originally filed.

Nos. NONE, as amended under Article 19.

Nos. NONE, filed with the demand.

Nos. NONE, filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig 1-6, as originally filed.

sheets/fig NONE, filed with the demand.

sheets/fig NONE, filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.

☒ the claims, Nos. NONE.

☒ the drawings, sheets/fig NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/10566

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)

Claims 3-13 YESClaims 1, 2 NO

Inventive Step (IS)

Claims NONE YESClaims 1-13 NO

Industrial Applicability (IA)

Claims 1-13 YESClaims NONE NO**2. CITATIONS AND EXPLANATIONS**

Claims 1-13 lack an inventive step under PCT Article 33(3) as being obvious over Crozier et al. Crozier et al. teach of increasing the dietary source of preformed 20 and 22 carbon long chain polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acid, to premature infants. The instant invention differs only in the specific range of dosages claimed. The determination of a dosage having the optimum therapeutic index is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Hence, the reference makes obvious the instant invention.

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by Crozier et al. Crozier et al. teach of increasing the dietary source of preformed 20 and 22 carbon long chain polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acid, to premature infants, (see Summary).

Claims 1-13 meet the criteria for Industrial Applicability under PCT Articles 33(4).

NEW CITATIONS

NONE

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International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 31/20</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/44917</b> <b>(43) International Publication Date:</b> 15 October 1998 (15.10.98)
<b>(21) International Application Number:</b> PCT/US98/10566 <b>(22) International Filing Date:</b> 20 March 1998 (20.03.98) <b>(30) Priority Data:</b> 60/042,366 27 March 1997 (27.03.97) US <b>(71) Applicant (for all designated States except US):</b> BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 06543 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SCHADE, Deborah, A. [US/US]; 8100 Upper Mt. Vernon Road, Evansville; IN 47712 (US). MERKEL, Kimberly, L. [US/US]; 6616 Whetstone Road, Evansville, IN 47711 (US). HANSEN, James, W. [US/US]; 5600 Spring Park Drive, Evansville, IN 47711 (US). <b>(74) Agents:</b> ROESLER, Judith, A. et al.; Mead Johnson Nutritional, 2400 West Lloyd Expressway, Mailcode A-21, Evansville, IN 47721 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> USE OF DOCOSAHEXANOIC ACID AND ARACHIDONIC ACID ENHANCING THE GROWTH OF PRETERM INFANTS		
<b>(57) Abstract</b>  A method for enhancing the growth of preterm infants involving the administration of certain long chain polyunsaturated fatty acids. It is preferred that the infants are administered an infant formula containing a combination of docohexaenoic acid and arachidonic acid.		

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/10566

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INNIS S.M.: "Essential fatty acid requirements in human nutrition" CAN.J.PHYSIOL.PHARMACOL., vol. 71, no. 9, September 1993, CANADA, pages 699-706, XP002073826 see abstract see page 705, right-hand column, last paragraph	1-13
X	CROZIER G.L. ET AL.: "Metabolism of long chain polyunsaturated fatty acids and infant nutrition" MONATSSCHRIFT FÜR KINDERHEILKUNDE, vol. 143, no. 7(SUPPL.2), 1995, GERMANY, pages 95-98, XP002073827 see abstract	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 August 1998

Date of mailing of the international search report

01/09/1998

Name and mailing address of the ISA  
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# INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CLANDININ M.T. ET AL.: "Assessment of the Efficacious Dose of Arachidonic Acids in Preterm Infant Formulas: Fatty Acid Composition of Erythrocyte Membrane Lipids" PEDIATRIC RESEARCH, vol. 42, no. 6, December 1997, USA, pages 819-825, XP002073828 see abstract see table 2 see table 3 see page 821, right-hand column, paragraph 3 - page 822, left-hand column, paragraph 1	1-13
X	KOLETZKO B. ET AL.: "Fette in der Ernährung von Neugeborenen mit niedrigem Geburtsgewicht" MONATSSCHRIFT FÜR KINDERHEILKUNDE, vol. 143, no. 7(suppl.2), 1995, GERMANY, pages 99-104, XP002073829 see abstract see page 103, middle column, line 31 - right-hand column, line 11	1-13
A	EP 0 231 904 A (MILUPA AG.) 12 August 1987 see the whole document	1-13

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/10566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0231904 A	12-08-1987	DE 3603000 A	06-08-1987

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## USE OF DOCOSAHEXANOIC ACID AND ARACHIDONIC ACID ENHANCING THE GROWTH OF PRETERM INFANTS

Field of Invention

The present invention concerns enhancing the growth of preterm infants involving administration of infant formula containing a combination of docosahexaenoic and arachidonic acid.

Background of the Invention

The long chain polyunsaturated fatty acids (LC PUFA) have been shown to be important in infant development. Particularly, arachidonic acid (ARA) and docosahexaenoic acid (DHA) are LC PUFA that are of special interest in infant nutrition because they are found in high concentrations in the brain (Sastry PS, Lipids of nervous tissue: composition and metabolism. Progress Lipid Res 1985;24:69-176) and the retina (Fliesler SJ and Anderson RE. Chemistry and metabolism of lipids in the vertebrate retina. Progress Lipid Res 1983;22:79-131). ARA (20:4n-6) and DHA (22:6n-3) are derived from the parent essential fatty acids linoleic acid (18:2n-6) and  $\alpha$ -linolenic acid (18:3n-3) through alternate desaturation and elongation and accumulate rapidly in fetal neural tissue during the last months of gestation and the first months of postnatal life (Makrides M, Neuman MA, Byard RW, Simmer K, Gibson RA. Fatty composition of the brain, retina and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189-94).

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Unlike term infants, preterm infants do not fully benefit from the maternal and placental LC PUFA supply during the last trimester of pregnancy. Even though preterm infants are capable of synthesizing both DHA and ARA from their 18 carbon precursors (Carnielli VP, Wattimena DJL, Luijendijk IHT, Boerlage A, Degenhart HJ, Sauer PJJ. The very low birth weight premature infant is capable of synthesizing arachidonic and docosahexaenoic acids from linoleic and linolenic acids. *Pediat Res* 1996;40:169-174), it remains unclear whether the rate of synthesis is adequate to meet the optimal needs for central nervous system accretion in the absence of a dietary supply of these fatty acids. Preterm infants are dependent on their own dietary supply of linoleic and  $\alpha$ -linolenic acids through either human milk, which also contains small but significant amounts of ARA and DHA or through commercially available artificial formulas, none of which in the United States contain ARA and DHA.

It has been demonstrated in recent studies (Hoffman DR and Uauy R. Essentiality of dietary  $\omega$ -3 fatty acids for premature infants: Plasma and red blood cell fatty acid composition. *Lipids* 1992;27:886-95) that the fatty acid composition of red blood cell membrane lipids in infants receiving formulas supplemented with DHA (0.35% of total fatty acids) was similar to human milk-fed infants. In the same study, Birch (Birch DG, Birch EE, Hoffman DR, Uauy RD. Retinal development in very-low-birth-weight infants fed diets differing in Omega-3 fatty acids. *Investigation Ophthalmology Visual Science* 1992;33:2365-76) found that retinal function improved with the provision of a dietary supply of DHA in very low birth weight infants.

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The first year growth of preterm infants fed standard formula compared to marine oil LC PUFA supplemented formula was studied by Carlson et al. (Carlson SE, Cooke, RJ, Werkman SH, Tolley EA. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. *Lipids* 1992;27:901-907). The experimental formulas provided 0.2% of total fatty acids as DHA and also provided 0.3% as EPA (20:5n-3). This EPA concentration is higher than found in human milk while the DHA level is similar to human milk. Beginning at 40 weeks from conception, marine oil supplemented infants compared to controls had significantly lower weight, length, and head circumference. From this study, Carlson (Carlson SE, Werkman SH, Peeles JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci USA* 1993;90:1073-77) hypothesized that dietary ARA could improve first year growth of preterm infants, in the context of restoring growth to the level of control formula containing no LC PUFA.

In another study (Montalto, FB, et al., *Pediatric Research*, Vol 39, page 316A, abstract no. 1878) it was shown that male infants fed marine oil supplemented formula (containing DHA but essentially no ARA) had, by 4 to 6 months, lower head circumference, length, weight and fat free mass than standard formula fed infants. A third study also showed decreased weight at 9 and 12 months corrected age in preterm infants fed marine oil supplemented formula (with LC PUFA) to 2 months corrected age compared with control formula containing no LC PUFA (Carlson SE, et al., *Am. J. Clin. Nutr.*, 63 pp 687-97, 1996).

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The prior art has demonstrated that infants with altered tissue LC PUFA levels, resulting from a lack of LC PUFA in their diets, may be at risk for neurological problems, may also have reduced scores on cognitive tests, and may have lower retinal development than human milk-fed infants. Worldwide regulatory organizations such as the WHO/FAO Expert Committee on Fats and Oils in Human Nutrition have recommended that LC PUFA be included in preterm infant formula. These recommendations have been made despite the negative effects observed of DHA supplements on growth. There has been no demonstration in the literature that ARA and DHA, particularly when added to infant formula, enhances the growth of infants above that demonstrated by control formulas not containing ARA and DHA.

#### Summary of the Invention

It has unexpectedly been discovered that preterm infants receiving infant formula supplemented with both DHA and ARA demonstrate enhanced growth. The present invention is directed to enhancing the growth of preterm infants comprising administering to said infants a growth enhancing amount of DHA and ARA.

#### Detailed Description of the Invention

As reported in a review of preterm infant growth by Carlson, SE, (The Jnl of Pediatrics, vol 125, pp 533-8, 1994) "After adjusting for postconceptional age, preterm infants show a decline (rather

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than a catch-up) in the normalized weight from approximately 2 to 4 months past expected term."

Several prior art studies have documented the value of administering DHA to infants. However, when DHA, either as the primary LC PUFA or combined with EPA, is administered to preterm infants, said infants suffer from decreased growth. It has been suggested that ARA may be beneficial to growth; however, heretofore the growth effects of administering both DHA and ARA to preterm infants have been unknown. It has been surprisingly discovered that administering the combination of ARA and DHA results in enhanced growth of infants relative to infants fed DHA alone. It has also been discovered that preterm infants administered an infant formula containing ARA and DHA exhibit enhanced growth relative to preterm infants fed control formula without DHA and ARA, such as those formulas currently used in modern nurseries. It has further been discovered that practice of the method of the invention results in growth of preterm infants catching up in an unexpected short time to a reference group of normal term breast fed infants.

The time to achieve growth similar or equivalent to normal term breast fed infants by practice of the method of the invention is less than 9 months corrected age; preferably less than 6 months corrected age, more preferably less than 4 months corrected age, even more preferably less than 2 months corrected age, and most preferably no greater than term corrected age.

The method of the invention requires a combination of DHA and ARA. The weight ratio weight of ARA:DHA can be about 1:2 to about 5:1, preferably about 1:1 to about 3:1, and more preferably

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about 2:1.

In the method of the invention the combination of DHA and ARA is preferably administered as part of an infant formula. The infant formula for use in the present invention is preferably nutritionally complete and typically contains suitable types and amounts of lipid, carbohydrate, protein, vitamins and minerals. The amount of lipid or fat typically can vary from about 3 to about 7 g/100 kcal. The amount of protein typically can vary from about 1 to about 5 g/100 kcal. The amount of carbohydrate typically can vary from about 8 to about 12 g/100 kcal. Protein sources can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, amino acids, and the like. Carbohydrate sources can be any used in the art, e.g., lactose, glucose, corn syrup solids, maltodextrins, sucrose, starch, rice syrup solids, and the like. Lipid sources can be any used in the art, e.g., vegetable oils such as palm oil, soybean oil, palmolein, coconut oil, medium chain triglyceride oil, high oleic sunflower oil, high oleic safflower oil, and the like. Conveniently, commercially available infant formula can be used. For example, Enfamil®, Enfamil® Premature Formula, Enfamil® with Iron, Lactofree®, Nutramigen®, Pregestimil®, ProSobee® (available from Mead Johnson & Company, Evansville, Indiana, U.S.A.), Similac®, Isomil®, Alimentum®, Neocare®, and Similac® Special Care (available from Ross Laboratories, Columbus, Ohio, U.S.A.), may be supplemented with suitable levels of ARA and DHA at the proper ratios and used in practice of the method of the invention.

The form of administration of the DHA and ARA in the method of the invention is not critical, as

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long as a growth enhancing amount is administered. Most conveniently, the DHA and ARA are supplemented into infant formula which is then fed to the infants. Alternatively, the DHA and ARA can be administered as a supplement not integral to the formula feeding, for example, as oil drops, sachets, in combination with other nutrient supplements such as vitamins, and the like.

The growth enhancing amount of DHA is typically about 2.5 mg/kg of body weight/day to about 60 mg/kg of body weight/day, preferably about 6 mg/kg of body weight/day to about 40 mg/kg of body weight/day, more preferably about 12 mg/kg body weight/day to about 30 mg/kg body weight/day, and even more preferably about 18 mg/kg of body weight/day to about 24 mg/kg of body weight/day.

The growth enhancing amount of ARA is typically about 5 mg/kg of body weight/day to about 120 mg/kg of body weight/day, preferably about 12 mg/kg of body weight/day to about 80 mg/kg of body weight/day, more preferably about 24 mg/kg body weight/day to about 60 mg/kg body weight/day, and even more preferably about 36 mg/kg of body weight/day to about 48 mg/kg body weight/day.

The amount of DHA in infant formulas for use in the present invention typically varies from about 2 mg/100 kilocalories (kcal) to about 50 mg/100 kcal, preferably about 5 mg/100 kcal to about 33 mg/100 kcal, more preferably about 10 mg/100 kcal to about 25 mg/100 kcal, and even more preferably about 15 mg/100 kcal to about 20 mg/100 kcal.

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The amount of ARA in infant formula for use in the present invention typically varies from about 4 mg/100 kcal to about 100 mg/100 kcal, preferably about 10 mg/100 kcal to about 67 mg/100 kcal, more preferably about 20 mg/100 kcal to about 50 mg/100 kcal, and even more preferably about 30 mg/100 kcal to about 40 mg/100 kcal.

The infant formula supplemented with oils containing DHA and ARA for use in the present invention can be made using standard techniques known in the art. For example, replacing an equivalent amount of an oil normally present, e.g., high oleic sunflower oil.

The source of the ARA and DHA can be any source known in the art such as fish oil, single cell oil, egg yolk lipid, brain lipid, and the like. The DHA and ARA can be in natural form, provided that the remainder of the LC PUFA source does not result in any substantial deleterious effect on the infant. Alternatively, the DHA and ARA can be used in refined form. It is preferred that the LC PUFA used in the invention contain little or no EPA. For example, it is preferred that the infant formulas used herein contain less than about 20 mg/100 kcal EPA; preferably less than about 10 mg/kcal EPA; more preferably less than about 5 mg/100 kcal EPA; and most preferably substantially no EPA.

Preferred sources of DHA and ARA are single cell oils as taught in U.S. patent nos. 5,374,657, 5,550,156, and 5,397,591, the disclosures of which are incorporated herein by reference in their entirety.

The following examples are to illustrate the invention but should not be interpreted as a limitation thereon.

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EXAMPLES

## I

CLINICAL STUDY DESIGN

## 1. INTRODUCTION

This study is a double-blind, randomized, controlled parallel design, prospective trial of premature infant formulas containing microalgae and fungi-derived oils which contain a part of their constituents arachidonic acid and docosahexaenoic acid. Formula feeding subjects will be randomized into one of 3 feeding groups:

- premature formula plus DHA (about 0.13% of energy) and ARA (about 0.26% of energy)
- premature formula plus DHA (about 0.13% of energy)
- premature formula WITHOUT DHA and ARA

The products have the same nutrient composition (see Appendix A) and differ only in the level of DHA and ARA. The products will be blinded. The present order of formula has no relationship to randomization.

Normal, term, breast fed infants will be enrolled to provide a normal visual acuity reference.

Fifty evaluable subjects will be completed in each group. Premature infants will remain on study formulas after reaching 90 kcal/kg/d for a minimum of 28 days or until hospital discharge whichever is longer. After 28 days or discharge, whichever is longer, all premature infants will receive Enfamil or Enfalac with Iron. If medically indicated, ProSobee, Lactofree, Alactamil, Nutramigen, or Pregestimil may be used in place of Enfamil or Enfalac with Iron. Term infants will receive at least 85% of their nutrition from breast milk. Primary measures of effectiveness will include visual acuity and red blood cell membrane fatty acid profiles (i.e. DHA and ARA levels). The measure of safety will be growth and adverse experience reports.

## 2. SUBJECTS

## 2.1 SOURCE AND CHARACTERIZATION OF STUDY GROUP

Acceptable preterm subjects will be relatively healthy premature infants taking

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preterm formula. Anticipated hospitalization should be sufficient to allow for 28 days of enteral intake  $\geq 90$  kcal/kg/d and  $\geq 85\%$  study formula intake. All races and both sexes will be eligible for the study.

## 2.2 INCLUSION CRITERIA

### Preterm infants

- . Birth weight  $\geq 900$  g
- . Formula feeding at time of study enrollment
- . Anticipate enteral intake of  $\geq 90$  kcal/kg/day for  $\geq 28$  days before discharge home
- . Informed consent obtained

### Term Infants:

- . 38 to 42 weeks gestation
- . Committed to breast feeding
- . Informed Consent obtained

## 2.3 EXCLUSION CRITERIA

### Preterm infants

- .  $\geq 1500$  g at birth

### Preterm and Term Infants:

- . History of underlying disease or congenital malformation which in the opinion of the investigator is likely to interfere with the evaluation of the subject
- . More than 24 days between birth and full oral feeds ( $\geq 90$  kcal/kg/d)
- . Small ( $<10$ th percentile) for gestational age at birth (SGA)
- . Necrotizing enterocolitis as diagnosed by the physician

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Other gastrointestinal disease

Impaired visual or ocular status at birth

## 2.4 CONCOMITANT MEDICATIONS, HOSPITALIZATIONS, ILLNESSES

No medication which may effect FPL response may be used within 3 days of measurement.

No evidence of viral or bacterial infection during FPL testing.

No medications known to effect lipid metabolism (e.g., heparin at therapeutic levels)

## 3. STUDY PRODUCT INFORMATION

### 3.1 FORMULATIONS

Nutrient composition is included as Appendix A.

## 4. STUDY PROCEDURES

### 4.2.1 ENROLLMENT

Enrollment will take place over a 6 month period. Ideally, sufficient subjects will be enrolled so that 10 subjects in each group complete the study at each site for the multi-center trial. A total of 50 infants per formula group will complete this trial.

### 4.2.2 SCHEDULE OF EVENTS (SEE FLOW CHART, SECTION 8.4)

#### 4.2.2.1 RECRUITMENT

Mothers of eligible, healthy, preterm formula fed infants and term, breastfed infants will be contacted, the study explained to them, and if they are agreeable, written informed consent obtained.

Term infants may be enrolled anytime from birth until or during the 48 week visit.

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#### 4.2.2.2 RANDOMIZATION

Recruited formula fed subjects will be randomized into study groups. Randomization can occur anytime after enteral feeds reach 50 kcal/kg/day until commencement of full enteral feeds (i.e.,  $\geq 90$  kcal/kg/day).

#### 4.2.2.3 FEEDING

All premature infants will receive their assigned study formula after informed consent has been granted and enteral feeds are at least 50 kcal/kg/day. The infant will remain on study formula 28 days after reaching 90 kcal/kg/d or until hospital discharge, whichever is longer. Oral feeding amount, strength and rate will advance as appropriate for the clinical management of the infant.

All parents will be instructed not to feed solid foods during the study. The parents will be instructed that the study formula or breast milk is to serve as the sole source of food from enrollment to study end.

#### 4.2.2.4 BASELINE DATA COLLECTION

The following data will be collected by the Investigator at the time of enrollment and randomization on the case report forms:

- . Informed consent of parent obtained.
- . Post conceptual age.
- . That the subject is a premature infant, with Birth weight  $\geq 900$  gm and  $\geq 1500$  gm or a normal term infant between 38 and 42 weeks gestational age.
- . That the preterm subject is receiving infant formula or term infant is committed to breast feeding.
- . Anticipated preterm infant enteral intake of  $\geq 90$  kcal/kg/day for  $\geq 28$  days prior to discharge home.
- . That the subject has no history of underlying disease, inborn error of metabolism, or congenital malformation which in the opinion of the Investigator is likely to interfere with the evaluation of the study formulas.

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That the subject is not small (<10th percentile) for gestational age at birth.

That the subject does not have necrotizing enterocolitis as diagnosed by a physician.

That the subject does not have a gastrointestinal disease.

No more than 24 days between birth and full enteral feeds (i.e.,  $\geq 90$  kcal/kg/day).

That the subject did not have impaired visual or ocular status at birth.

Birth date, sex, race.

Birth weight, length and head circumference

#### 4.2.2.5 INVESTIGATOR PERIODIC DATA COLLECTION

"During hospitalization, preterm subjects will have their weight recorded daily while they are receiving study formula. Length and head circumference will be recorded weekly, along with an additional weight measurement. For a given subject, the same scale should be used for the weekly weight measurement."

"Weight, length, and head circumference will also be recorded at the 40, 48, and 57 week post conceptual age visit (preterm) and 56 and 119 days of age visit (term)."

#### 4.2.2.6 BLOOD DRAW

When preterm infant enrolls in the study and again at termination of study formula (i.e., hospital discharge or 28 days after reaching 90 kcal/kg/d of study product), the Investigator will ascertain that the infant is essentially solely formula fed. If this criteria is met, 1.2 ml/blood will be drawn for blood lipids. The sample will be processed as described in Appendix B.

An attempt will also be made to draw a similar blood sample at the 48 weeks PCA visit when visual acuity is measured in both term and preterm infants.

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#### 4.2.2.7 VISUAL ACUITY BY FORCED CHOICE PREFERENTIAL LOOKING (FPL) AT 48 AND 57 WEEKS $\pm$ 4 DAYS POST-CONCEPTUAL AGE

When the infant is 48 and 57 weeks  $\pm$  4 days post-conceptual age, trained persons at each study site will follow the Teller Acuity Card Procedure for the measurement of visual acuity of all study subjects. It is essential that only persons who are trained in the FPL procedure for determining visual acuity do the testing. If necessary, training of responsible persons and documentation of completion of successful training will be done at Children's Hospital Medical Center Ophthalmology Department in Seattle, Washington, according to the procedure attached as Appendix C.

If the infant cannot complete the procedure at 48 or 57 weeks  $\pm$  4 days postconceptual age (i.e., too fussy, too sleepy, too inattentive) the test should be repeated within 7 days.

#### 4.2.2.8 INTERIM EVALUATION

At preterm infant hospital discharge or 28 days after reaching 90 kcal/kg/d of study formula feeding, whichever is longer, the investigator will fill out an "Interim Evaluation" form. After reviewing the subject's records and discussion with the parents and staff, the investigator will indicate whether:

- Whether or not the subject completed at least 28 days of study formula intake  $\geq$  90 kcal/kg/d and both blood samples obtained

- If the study was not completed, and reason

- Whether or not the subject received steroids (glucocorticoids)

- Investigator's evaluation of the study formula

The first and last dates study material was taken will be recorded.

#### 4.2.2.9 FINAL EVALUATION

At the final study visit (57 weeks postconceptual age) or earlier if the subject drops out, the Investigator will fill out a "Final Evaluation" Case Report Form. After reviewing the subject's records and discussion with the parents, the Investigator will indicate whether the subject:

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- (1) Completed feeding regiment and all study parameters (i.e., anthropometrics and visual acuity measured).
- (2) Did not complete feeding regimen.
- (3) Not completed and reason.

#### 4.3 CLINICAL OBSERVATIONS

##### 4.3.1 PHYSICAL EXAMINATIONS

Subjects will have weight, length and head circumferences recorded at birth, weekly while hospitalized, then at 40, 48, and 57 weeks  $\pm$  4 days postconceptual age.

Body weight will be measured using an electronic balance or a double beam balance accurate to 10 g or  $\frac{1}{2}$  oz with non-detachable weights. During hospitalization, if more than one such balance is employed in the practice, either one balance should be designated the study balance and all study weights will be carried out on that balance for a particular subject, or the balances will be checked and certified to register the same weight throughout the range of weights expected. Outpatient weights will be obtained on a calibrated office scale.

Documentation indicating balance calibration of the outpatient balance carried out within 12 months of study initiation will be supplied to the Sponsor.

Length will be measured with the infant in recumbent position with the help of two examiners and a suitable measuring apparatus. One person holds the subject's head in contact with a fixed vertical headboard and a second person holds the subject's feet, toes pointing directly upward and, also applying gentle traction. The baby is measured from the headboard to the soles of the feet with a non-stretching tape measure.

Head circumference will be measured, employing a flexible, non-stretchable cloth or vinyl tape.

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4.3.2 VISUAL ACUITY BY FORCED CHOICE PREFERENTIAL  
LOOKING (FPL)

Visual acuity will be determined at 48 and 57 weeks  $\pm$  4 days postconceptual age according to procedures outlined in Appendix C.

4.3.3 LABORATORY TESTS

Blood will be drawn from preterm infants by heel prick or venipuncture when study formula is begun and terminated. An attempt will be made to draw blood at 48 weeks  $\pm$  4 days PCA from both term and preterm infants. Procedures for handling the blood are described in Appendix B.

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## 4.4 FLOW CHART

EVENT	PRETERM						TERM		
	Birth	Enteral Intake >50 kcal/kg/d	Termination of Study Formula †	Visit 1 40 wks ± 4d PCA	Visit 2 48 wks ± 4d PCA	Visit 3 57 wks ± 4d PCA	Visit 1 40 wks ± 4d PCA	Visit 2 48 wks ± 4d PCA	Visit 3 57 wks ± 4d PCA
Randomization		✓							
Study Formula		✓							
Entamil w/iron			✓	✓	✓	✓			
Human Milk							✓	✓	✓
	Physical						Physical		
Weight	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Length	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Head Circumference	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Blood Draw		✓	✓		✓			✓	
Visual Acuity Test					✓	✓		✓	✓
ILLNESSES Parental Concerns				✓	✓	✓		✓	✓
Interim Assessment			✓						
Final Assessment							(when the subject discontinues or completes)		

Medical problems related to or affecting formula consumption will be recorded when they occur.

Recorded weekly during hospitalization

At hospital discharge or 28 days of study formula intake (after reaching 90 kcal/kg/d), whichever is later

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## 5. CRITERIA FOR RESPONSE

Criteria for response will depend upon the following:

Visual Acuity better than the control formula.

Visual Acuity comparable to breastfed term infant.

Red Blood Cell phosphatidyl ethanolamine DHA and ARA weight % greater than formula control group.

Growth as measured by weight achieved at 48 and 57 weeks postconceptual age comparable to formula control group.

## 6. STATISTICS

### 6.1 RANDOMIZATION

If the subject meets the inclusion and exclusion criteria, randomization to one of three formula groups will take place. The randomization schedule will be provided by Mead Johnson Research Center. A separate randomization schedule will be provided for males and females.

### 6.2 SAMPLE SIZE

The primary parameter of interest is visual acuity as measured by the Forced Choice Preferential Looking (FPL). The minimal clinically relevant difference was determined to be 0.5 octave. A consultant in the field of visual acuity estimated the standard deviation to be 0.5 octave. This value was increased to .7 octave in case more variability was experienced in this study. Thirty-two subjects per group are needed to attain 80% power when testing at an alpha level of 0.05.

A sample size estimate of 50 per group was determined to achieve  $\alpha + 0.05$ ,  $\beta + 0.20$ , for weight of infants receiving study oil being greater than 400 gm below control at 48 weeks postconceptual age or 500 g below control at 57 weeks postconceptual age with a standard deviation of 800 g. It was therefore determined that 50 subjects per group will be used in the study.

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### 6.3 ANALYTICAL PLAN

Visual acuity data will be recorded in cycles per cm. These values will be converted to cycles per degree using the following formula:

$$\text{cycles/degree} = \frac{38 \times \text{cycles/cm}}{55}$$

A log transformation will be applied to the data prior to analysis. Analysis of variance techniques will be used to assess feeding regimen group differences in visual acuity. If the overall F test for feeding regimen is significant at an alpha level of 0.05, pairwise comparisons will be made at an alpha level of 0.05. If no significant differences are detected, then a post-study power analysis will be performed to demonstrate that the study had adequate power to detect the minimal clinically relevant difference.

Analysis of variance will be used to assess feeding regimen differences in phosphatidyl choline DHA and ARA levels and in phosphatidyl ethanolamine DHA and ARA levels at each time point. If the overall F test is significant at an alpha level of 0.05, then pairwise comparisons will be made at an alpha level of 0.05.

Analysis of variance will be used to assess feeding regimen differences in weight at 48 and 57 weeks postconceptual age. The statistical model will include terms for feeding regimen, study center, sex and all two-way interactions. Non-significant interactions will be removed from the final statistical model. Two one-sided tests will be performed comparing each experimental formula (EC) with the control formula (CF). The hypothesis to be tested is as follows:

$$H_0 = \text{Weight (CF)} \leq \text{Weight (EF)}.$$

The alternative hypothesis is as follows:

$$H_1 = \text{Weight (CF)} > \text{Weight (EF)}.$$

If  $H_0$  is rejected and the mean weight of the control formula exceeds that of the experimental formula by more than 400 mg at 48 weeks postconceptual age or by 500 g at 57 weeks postconceptual age then the conclusion is that the experimental formula does not exceed that of the experimental formula by more than 400 g at 48 weeks postconceptual age

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or by 500 mg at 57 weeks postconceptual age then the conclusion is that the experimental formula does provide adequate growth. If  $H_0$  is not rejected then a post-study power analysis will be performed to demonstrate that the study had adequate power to detect the above mentioned clinically relevant differences. If adequate power is achieved then the conclusion is that the experimental formula does provide adequate growth.

Fisher's exact test will be used to compare the proportion of subjects in each group with illness/symptoms of concern during the study. The analysis will be performed for each type of illness/symptom reported, with classification of investigator terms into similar terminology made as necessary.

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## APPENDIX A

### NUTRIENT COMPOSITION OF FORMULAS

All study formulas are 24 kcal/fl oz and are identical in composition to marketed Enfamil Premature Formula except for the study oils employed. These oils are described in the protocol.

NUTRIENT	STUDY FORMULAS AMOUNT/100 kcal	ENFAMIL WITH Fe
Protein, g	3	2.2
Fat, g	5.1	5.6
Carbohydrate, g	11.1	10.3
Vitamin A IU	1250	310
Vitamin D IU	270	63
Vitamin E IU	6.3	2
Vitamin K mcg	8	8
Thiamine, mcg	200	78
Riboflavin, mcg	300	150
Vitamin B <sub>6</sub> , mcg	150	63
Vitamin B <sub>12</sub> , mcg	0.25	0.23
Niacin, mcg	4000	1250
Folic Acid, mcg	35	15.6
Pantothenate, mcg	1200	470
Biotin, mcg	4	2.3
Vitamin C, mg	20	8.1
Choline, mg	12	15.6
Inositol, mg	17	4.7
Calcium, mg	165	78
Phosphorus, mg	83	53
Magnesium, mg	6.3	7.8
Iron, mg	1.8	0.5
Zinc, mg	1.5	0.78
Manganese, mcg	6.3	15.6
Copper, mcg	125	94
Iodine, mcg	25	6
Sodium mg (mEq)	39 (1.7)	27(1.17)
Potassium mg (Meq)	103 (2.6)	108 (2.8)
Chloride mg (Meq)	85 (2.4)	63 (1.77)

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## II

## FINAL STUDY REPORT

**Study Design:** This double-blind, parallel-group study (project 3338) was carried out in 16 neonatal centers (study numbers 9698-9709, 9712, 9723, 9743, and 9746) in North America. Three premature infant feedings were compared. Each had the same composition except for the incorporation of fungal and/or micro algal oils up to about 3% of the fat blend to provide the experimental levels of docosahexaenoic acid (DHA) and arachidonic acid (ARA). The control formula (C, Enfamil® Premature Formula) contained no DHA or ARA, the DHA formula (D) contained about 0.15% of energy as DHA (0.34% of fat), and the DHA+ARA formula (DA) contained about 0.14% of energy as DHA (0.33% of fat) and 0.27% of energy as ARA (0.60% of fat). The formulas were fed to 284 randomized infants weighing 846 to 1560 grams at birth for at least 28 days. Upon completion of study formula intake, they were given routine infant formula and followed through 4 months gestationally corrected age. A group of 90 exclusively human milk fed term infants were enrolled and followed to 4 months of age as a reference group (H).

**Study Objective and Statistical Analysis:** The primary objective of this study was to establish the safety of feeding D or DA to preterm infants during their initial hospitalization as measured 1) by growth, acceptance and tolerance while consuming the formula for at least 1 month and 2) by close monitoring and observation for a 4 to 5 month follow-up period (4-5 times the treatment period) while consuming unsupplemented routine term infant formula. The primary growth parameter selected was weight with evaluation of the proposition that weight on test formula was greater than or equal to weight on control formula. The one sided statistical test for an adverse effect on growth maximized the power to detect a difference should one be present. A two-sided test was used for all other parameters. A p-value of less than 0.05 was used to establish significance.

Secondary objectives of the study were 1) to evaluate the impact of fatty acid levels in erythrocyte phospholipids at the end of study feeding and 2) to determine if any effect on mean visual acuity greater than half an octave could be demonstrated at 2 and 4 months corrected age.

**Results:** Six infants were just outside the weight parameters and five infants just older than the less than 24 days chronological age parameter for enrollment in the study. In each case, judgement by the clinical or medical monitor was made to include them in the study prior to enrollment based on their homogeneity with other study infants in all other particulars, e.g., state of health, type of medical complications, and weight for gestational age. All these infants were included in the analysis of the study results.

The formula groups were comparable at enrollment (See table 1). Post-conceptual age, weight, length, and head circumference at enrollment did not differ among the groups.

All groups experienced comparable final study status (See table 2). Drop outs did not differ among the formula fed groups during hospitalization. There also were no differences in drop outs among the four groups at study completion.

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Both formulas D and DA provide adequate growth when compared to formula C (See table 3, figure 1, and Appendix 1). Weight gain during hospitalization was no less on D or DA than on C, 33.3, 34.7, and 30.7 g/day, respectively. Furthermore, no less weight was achieved on D or DA than on C at 40, 48, and 57 weeks post-conceptual age (See table 4, figure 2, and Appendix 1); statistical power was greater than 0.89 to detect a clinically relevant decrease.

Post-hoc analysis reveals that infants on DA grew faster than infants receiving C and D (See table 5 and figure 1). This enhanced growth provided faster "premature infant catch-up" compared to C and D. Weight achieved by the DA group (3198 g) was higher than C (3075 g) and D (3051 g) at 40 weeks post-conceptual age but had not fully caught up to the term birth weight (3438 g) of group H (See table 4 and figure 2). This catch up trend continued through 48 to 57 weeks by which time the mean weight of group DA did not differ from group H while groups C and D remained significantly lower.

Length was not different among the formula groups either during hospitalization or the follow-up period, although the ordered sequence of mean lengths was the same as for the weights (See table 7 and figure 3). This is likely at least partially due to length being a less sensitive parameter of growth than weight. For the same reason, the mean lengths of group H infants were higher than that of all the premature infant groups at 40, 48 and 57 weeks post-conceptual age indicating slower catch up in this parameter.

Head circumference is the least sensitive parameter of growth and was not different among any of the four groups at any time measured except at 40 weeks postconceptual age (See table 8 and figure 4). At this time, as expected, the birth head circumference of group H was smaller than the formula fed premature infants possibly due to molding of labor and to insufficient time for adjustment to the extrauterine environment.

Visual acuity has reportedly been enhanced in studies where DHA supplemented formulas were fed to premature infants both in the hospital and continuing after discharge. In this study, visual acuity was measured about 3 months and then about 5 months after stopping study formula to determine whether a residual beneficial effect of at least half an octave might be observed. Although no difference in visual acuity was found among the formula groups at these times (See table 8 and figure 5), the acuity card method used, the length of study formula feeding, and/or the length of time not on study formula at the time of measurement may have precluded its detection. However, at 57 weeks post-conceptual age, the breast fed term infant group did have statistically higher visual acuity scores than the test formula groups. But even these differences were at most only 0.33 octave and were clinically insignificant (See figure 6). It is important to note that the breast fed infants continued to receive DHA and ARA during the 3-5 month follow-up period while the formula fed groups did not. Thus, this minor difference in performance was not unexpected based on previous study findings and on developmental differences between term and preterm infants even at the same gestational age.

Individual fatty acid levels were determined in the phosphatidylcholine and phosphatidylethanolamine fractions of red blood cells before formula feeding, at the conclusion of test formula feeding, and at 48 weeks post-conceptual age (See tables 9 and 10). The premature infant groups were comparable at the beginning of test formula feeding. At the conclusion of test

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formula feeding, individual fatty acid levels varied among the groups. DHA and ARA were statistically significantly higher in the respectively supplemented groups. Other fatty acid levels reflected the impact of the supplementation. No clinically significant alterations in fatty acid levels or metabolism were identified. After discontinuing study formula and consuming a diet without DHA or ARA for about 3 months, no differences in fatty acid levels among formula fed groups were detectable, except for phosphatidylethanolamine levels of 18:2 (range 8.9-9.3%) and DHA (range 3.2-4.1%) which differences were not identified as being clinically significant. However, the breast fed group shows statistically significant differences in 13 fatty acid levels compared to the formula fed infants. These differences are undoubtedly due to the differences in fatty acid composition of human milk and the term formulas including the lack of DHA and ARA in the latter.

Preterm infant complications were similar in all groups (See table 11). Over 80% of all infants were ophthalmologically examined and over 90% had ultrasound evaluation of their heads. Specifically, the incidence and severity of retinopathy of prematurity (ROP or retrolental fibroplasia/RLF) and the incidence of intraventricular hemorrhage or its complications did not differ among formula groups. No feeding group related complications were identified.

Serious adverse experiences did not differ ( $p=0.93$ ) among the formula groups and were in the range of those expected in a premature infant population while on study formula: 6% in group C, 5% in group D, and 6% in group DA (See table 12). After the experimental formula phase, serious adverse experiences still did not differ among the preterm groups (See table 13): 13% in group C, 15% in group D, and 15% in group DA. However, the term infant breast fed group had significantly fewer serious adverse experiences (1%,  $p=0.002$ ) as expected. Two infants reportedly suffered sudden infant death syndrome (SIDS), one in group C and one in group D; there was no significant difference in this complication among all four groups.

**Conclusions:** We conclude that feeding 0.13% of calories as DHA from micro algal oil and feeding 0.13 % of calories as DHA from micro algal oil plus 0.26% of calories as ARA from fungal oil in the matrix of premature infant formula to premature infants during the period of their initial hospitalization prior to 40 weeks post conceptual age is safe. These micro algal and fungal oil supplements do not result in any adverse effect on growth, clinical complications, or untoward events. Furthermore, this study reveals that growth benefits accrue to premature infants fed Enfamil Premature Formula supplemented with DHA and ARA from these sources compared to unsupplemented formula or formula supplemented with only DHA. No measurable benefit on visual acuity was identified when infants were tested at about 3 and 5 months after the supplemented formula was discontinued (2 and 4 months corrected age). However, providing human milk levels of intake of long chain polyunsaturated acids are warranted because they are critical to brain development and foster enhanced catch-up growth during this early development period.

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Table 1  
Birth Statistics of Premature Subjects

	n	Mean (std)	Range	p-value
Post-Conceptual Age (Weeks)				
Control	62	29.5 (1.7)	25 - 33	0.076
DHA	66	30.0 (1.4)	26 - 32	
DHA+ARA	66	29.7 (1.7)	26 - 34	
Birth Weight (g)				
Control	62	1233.1 (176.6)	846 - 1560	0.25
DHA	66	1272.8 (168.1)	900 - 1545	
DHA+ARA	66	1278.9 (177.6)	910 - 1535	
Birth Length (cm)				
Control	60	38.4 (2.3)	34 - 43.75	0.62
DHA	66	38.6 (2.2)	33 - 43.5	
DHA+ARA	66	38.7 (2.3)	33 - 44	
Birth Head Circumference (cm)				
Control	61	26.9 (1.5)	23.5 - 30.5	0.53
DHA	64	27.3 (2.1)	22 - 37	
DHA+ARA	65	27.2 (1.6)	23.5 - 30	

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Table 2  
Summary of Final Study Status

	Regimen				p-value
	Control	DHA	DHA+ARA	HM	
Immediate dropout, study formula never consumed		2	2		
Study Formula Phase *					0.20
Completed	52 (84%)	59 (89%)	62 (94%)		
Discontinued	10 (16%)	7 (11%)	4 (6%)		
Reason discontinued					
>96 cumulative hours NPO	3	1			
<28 days of intake $\geq$ 90 kcal/kg/day	3	3			
Complications unrelated to study formula	1				
NEC or other GI disease		1	1		
Formula intolerance			1		
Parents request	2	2	1		
Not off oxygen prior to discharge			1		
Protocol violation	1				
Term Formula Phase **					0.74
Completed	45 (87%)	47 (80%)	53 (85%)	77 (86%)	
Discontinued	7 (13%)	12 (20%)	9 (15%)	13 (14%)	

\*The CRFs for 9709-003 (DHA) and 9743-304 (DHA) were marked discontinued because the subjects met the study formula intake criteria for only 27 days. These subjects are counted completed here because subjects at other sites with similar intakes were marked completed.

\*\*Based on subjects who completed the Study Formula phase. During the Term Formula phase, subjects were fed marketed formula. Switching to a different marketed formula did not result in termination from the Term Formula phase.

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Table 3

Weight Growth Rate During Study Formula Phase							
Regimen	n	Least Square Mean	Standard Error	Comparison	Comparison p-value*	Study p-value	Gender p-value
Control	60	30.7	1.1	Control vs DIA	0.967	0.00	0.17
DIA	65	33.3	1.1	Control vs DIA+ARA	0.998		
DIA+ARA	66	34.7	1.1				0.87

\* One-sided test of the null hypothesis: Test Mean &gt;= Control Mean

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Table 4  
Weight at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Comparison	Comparison p-value*	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	52	3075.3	67.9	Control vs DHA	0.388	0.59	0.45	1.00
	DHA	54	3051.4	66.8	Control vs DHA+ARA	0.931			
	DHA+ARA	59	3198.2	62.9	HM vs DHA	0.000			
	HM	90	3437.7	60.6	HM vs DHA+ARA HM vs Control	0.001 0.000			
48	Control	53	4711.0	94.6	Control vs DHA	0.360	0.58	0.13	0.29
	DHA	51	4663.8	97.3	Control vs DHA+ARA	0.995			
	DHA+ARA	57	5039.1	93.0	HM vs DHA	0.000			
	HM	81	5181.5	85.9	HM vs DHA+ARA HM vs Control	0.114 0.000			
57	Control	47	6045.4	139.5	Control vs DHA	0.371	0.58	0.29	0.33
	DHA	49	5987.2	137.6	Control vs DHA+ARA	0.940			
	DHA+ARA	55	6312.9	127.9	HM vs DHA	0.005			
	HM	76	6405.0	126.7	HM vs DHA+ARA HM vs Control	0.278 0.014			

\* One-sided test of the null hypothesis: Test Mean >= Control Mean

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Table 5  
Post-hoc Analysis of Weight

Time	Comparison	Two-sided p-value
Weight Gain During Study Formula Phase	C vs. DHA	0.067
	C vs. DHA+ARA	0.004
	DHA vs. DHA+ARA	0.30
Weight at 40 Weeks pca	C vs. DHA	0.78
	C vs. DHA+ARA	0.14
	DHA vs. DHA+ARA	0.074
	HM vs. DHA	<0.001
	HM vs. DHA+ARA	0.002
Weight at 48 Weeks pca	HM vs. C	<0.001
	C vs. DHA	0.72
	C vs. DHA+ARA	0.011
	DHA vs. DHA+ARA	0.004
	HM vs. DHA	<0.001
Weight at 57 Weeks pca	HM vs. DHA+ARA	0.23
	HM vs. C	<0.001
	C vs. DHA	0.74
	C vs. DHA+ARA	0.12
	DHA vs. DHA+ARA	0.057
	HM vs. DHA	0.010
	HM vs. DHA+ARA	0.56
	HM vs. C	0.028

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Table 6  
Length at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	52	48.4	0.4	0.000	Control vs DHA	0.242	0.03	0.88	0.63
	DHA	54	47.8	0.4		Control vs DHA+ARA	0.233			
	DHA+ARA	58	49.0	0.4		HM vs DHA	0.000			
	HM	89	50.6	0.4		HM vs DHA+ARA	0.000			
48	Control	53	54.7	0.3	0.000	Control vs HM	0.000	0.00	0.14	0.52
	DHA	52	54.6	0.3		DHA vs DHA+ARA	0.824			
	DHA+ARA	57	55.5	0.3		Control vs DHA	0.079			
	HM	81	57.4	0.3		HM vs DHA	0.000			
57	Control	47	60.7	0.4	0.000	Control vs DHA	0.615	0.00	0.02	0.84
	DHA	49	60.5	0.4		Control vs DHA+ARA	0.236			
	DHA+ARA	54	61.3	0.3		HM vs DHA	0.000			
	HM	76	62.4	0.3		HM vs DHA+ARA	0.006			
						Control vs HM	0.000			
						DHA vs DHA+ARA	0.087			

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Table 7  
Head Circumference at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	51	35.4	0.2	0.000	Control vs DHA	0.931	0.91	0.00	0.38
	DHA	53	35.4	0.2		Control vs DHA+ARA	0.900			
	DHA+ARA	58	35.5	0.2		HH vs DHA	0.000			
	HH	85	34.5	0.2		HH vs DHA+ARA	0.000			
48	Control	52	39.1	0.2	0.983	Control vs HH	0.000	0.81	0.00	1.00
	DHA	51	39.0	0.2		DHA vs DHA+ARA	0.829			
	DHA+ARA	56	39.0	0.2						
	HH	81	39.0	0.1						
57	Control	47	41.9	0.2	0.689			0.64	0.00	0.85
	DHA	49	41.6	0.2						
	DHA+ARA	53	41.7	0.2						
	HH	76	41.7	0.2						

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Table 8

Visual Acuity at 48 and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Geometric mean (cycles/deg)	Least Square Mean (log base2 cycles/deg)	Standard Error (octaves)	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value
48	Control	51	1.72	0.78	0.10	0.950			0.000
	DHA	50	1.80	0.85	0.10				
	DHA+ARA	57	1.72	0.78	0.09				
	HM	81	1.75	0.81	0.09				
57	Control	46	3.47	1.79	0.08	0.004	Control vs DHA	0.697	0.000
	DHA	47	3.37	1.75	0.08		Control vs DHA+ARA	0.071	
	DHA+ARA	55	3.06	1.61	0.07		HM vs DHA	0.042	
	HM	77	3.85	1.94	0.07		HM vs DHA+ARA Control vs HM DHA vs DHA+ARA	0.000 0.113 0.158	

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	12:0	Control	52	0.081	0.019	0.036	0.762		
		DHA	58	0.066	0.013	0.030			
		DHA+ARA	61	0.057	0.009	0.031			
Study Form Initiation	14:0	Control	52	0.623	0.036	0.599	0.559		
		DHA	58	0.663	0.031	0.686			
		DHA+ARA	61	0.661	0.031	0.656			
Study Form Initiation	14:1	Control	52	0.045	0.009	0.021	0.165		
		DHA	58	0.026	0.005	0.016			
		DHA+ARA	61	0.035	0.006	0.018			
Study Form Initiation	16:0	Control	52	36.706	0.540	36.594	0.884		
		DHA	58	36.363	0.462	35.578			
		DHA+ARA	61	36.877	0.445	35.987			
Study Form Initiation	16:1	Control	52	0.940	0.049	0.845	0.441		
		DHA	58	0.981	0.050	0.976			
		DHA+ARA	61	1.094	0.064	0.931			
Study Form Initiation	18:0	Control	52	11.660	0.243	11.468	0.243		
		DHA	58	11.402	0.238	11.201			
		DHA+ARA	61	11.016	0.192	11.174			
Study Form Initiation	18:1	Control	52	17.053	0.298	17.308	0.679		
		DHA	58	17.219	0.391	16.935			
		DHA+ARA	61	17.256	0.271	16.988			
Study Form Initiation	18:2	Control	52	18.614	0.525	18.952	0.830		
		DHA	58	18.631	0.505	19.603			
		DHA+ARA	61	18.573	0.466	18.824			
Study Form Initiation	18:3n6	Control	52	0.120	0.008	0.116	0.034	Control vs DHA	0.196
		DHA	58	0.136	0.008	0.130		Control vs DHA+ARA	0.010
		DHA+ARA	61	0.150	0.009	0.134		DHA vs DHA+ARA	0.176

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	20:0	Control	52	0.399	0.050	0.224	0.647		
		DHA	58	0.337	0.035	0.236			
		DHA+ARA	61	0.310	0.037	0.188			
Study Form Initiation	18:3n3	Control	52	0.315	0.033	0.246	0.234		
		DHA	58	0.257	0.014	0.246			
		DHA+ARA	61	0.233	0.010	0.216			
Study Form Initiation	20:1	Control	52	0.287	0.020	0.262	0.723		
		DHA	58	0.287	0.015	0.281			
		DHA+ARA	61	0.268	0.011	0.269			
Study Form Initiation	18:4	Control	52	0.017	0.003	0.000	0.290		
		DHA	58	0.025	0.004	0.017			
		DHA+ARA	61	0.017	0.003	0.008			
Study Form Initiation	20:2n6	Control	52	0.632	0.025	0.632	0.673		
		DHA	58	0.628	0.025	0.640			
		DHA+ARA	61	0.602	0.021	0.614			
Study Form Initiation	20:3n6	Control	52	2.144	0.098	2.096	0.507		
		DHA	58	2.208	0.080	2.296			
		DHA+ARA	61	2.218	0.074	2.135			
Study Form Initiation	20:4n6	Control	52	7.657	0.262	8.124	0.819		
		DHA	58	8.164	0.347	7.876			
		DHA+ARA	61	8.090	0.310	8.207			
Study Form Initiation	22:1	Control	52	0.106	0.010	0.105	0.155		
		DHA	58	0.127	0.010	0.130			
		DHA+ARA	61	0.126	0.010	0.139			
Study Form Initiation	20:5n3	Control	52	0.351	0.057	0.298	0.911		
		DHA	58	0.322	0.015	0.302			
		DHA+ARA	61	0.321	0.015	0.329			

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Table 9  
Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	22:4n6	Control	52	0.578	0.144	0.423	0.331		
		DHA	58	0.493	0.030	0.481			
		DHA+ARA	61	0.443	0.021	0.425			
Study Form Initiation	24:1	Control	52	0.208	0.054	0.075	0.665		
		DHA	58	0.115	0.019	0.084			
		DHA+ARA	61	0.180	0.056	0.096			
Study Form Initiation	22:5n6	Control	52	0.266	0.020	0.232	0.923		
		DHA	58	0.259	0.017	0.239			
		DHA+ARA	61	0.265	0.018	0.256			
Study Form Initiation	22:4n3	Control	52	0.000	0.000	0.000	0.199		
		DHA	58	0.001	0.001	0.000			
		DHA+ARA	61	0.002	0.001	0.000			
Study Form Initiation	22:5n3	Control	52	0.213	0.019	0.203	0.885		
		DHA	58	0.215	0.013	0.195			
		DHA+ARA	61	0.203	0.010	0.193			
Study Form Initiation	22:6n3	Control	52	0.984	0.051	1.000	0.858		
		DHA	58	1.075	0.053	1.034			
		DHA+ARA	61	1.006	0.050	0.970			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	12:0	Control	53	0.100	0.026	0.035	0.843		
		DHA	56	0.111	0.042	0.031			
		DHA+ARA	59	0.064	0.012	0.032			
Study Form Termination	14:0	Control	53	0.808	0.039	0.806	0.834		
		DHA	56	0.781	0.035	0.783			
		DHA+ARA	59	0.755	0.036	0.758			
Study Form Termination	14:1	Control	53	0.047	0.008	0.033	0.155		
		DHA	56	0.036	0.009	0.015			
		DHA+ARA	59	0.036	0.007	0.018			
Study Form Termination	16:0	Control	53	35.837	0.512	34.798	0.767		
		DHA	56	35.560	0.595	34.841			
		DHA+ARA	59	35.069	0.584	33.890			
Study Form Termination	16:1	Control	53	0.566	0.026	0.526	0.013	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.118 0.003 0.152
		DHA	56	0.594	0.042	0.475			
		DHA+ARA	59	0.526	0.029	0.472			
Study Form Termination	18:0	Control	53	13.972	0.261	14.197	0.886		
		DHA	56	14.065	0.237	13.867			
		DHA+ARA	59	14.341	0.253	14.108			
Study Form Termination	18:1	Control	53	14.456	0.277	14.291	0.886		
		DHA	56	14.116	0.272	13.998			
		DHA+ARA	59	14.344	0.380	14.218			
Study Form Termination	18:2	Control	53	21.673	0.340	21.506	0.001	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.600 0.005 0.001
		DHA	56	22.045	0.457	22.517			
		DHA+ARA	59	19.899	0.337	20.662			
Study Form Termination	18:3n6	Control	53	0.080	0.006	0.074	0.527		
		DHA	56	0.088	0.009	0.076			
		DHA+ARA	59	0.087	0.013	0.066			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	20:0	Control	53	0.504	0.050	0.392	0.424		
		DHA	56	0.472	0.053	0.281			
		DHA+ARA	59	0.430	0.049	0.251			
Study Form Termination	18:3n3	Control	53	0.321	0.020	0.283	0.031	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.503 0.068 0.011
		DHA	56	0.335	0.030	0.285			
		DHA+ARA	59	0.273	0.009	0.256			
Study Form Termination	20:1	Control	53	0.318	0.014	0.302	0.149		
		DHA	56	0.300	0.013	0.283			
		DHA+ARA	59	0.307	0.013	0.283			
Study Form Termination	18:4	Control	53	0.022	0.004	0.015	0.672		
		DHA	56	0.022	0.003	0.018			
		DHA+ARA	59	0.014	0.002	0.008			
Study Form Termination	20:2n6	Control	53	0.893	0.026	0.910	0.051		
		DHA	56	0.880	0.023	0.873			
		DHA+ARA	59	0.824	0.022	0.821			
Study Form Termination	20:3n6	Control	53	2.032	0.073	2.091	0.208		
		DHA	56	2.017	0.070	2.043			
		DHA+ARA	59	1.908	0.064	1.904			
Study Form Termination	20:4n6	Control	53	6.046	0.240	6.029	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.097 0.000 0.000
		DHA	56	5.774	0.220	5.892			
		DHA+ARA	59	8.465	0.255	8.891			
Study Form Termination	22:1	Control	53	0.117	0.010	0.125	0.946		
		DHA	56	0.110	0.009	0.114			
		DHA+ARA	59	0.115	0.011	0.104			
Study Form Termination	20:5n3	Control	53	0.214	0.022	0.189	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.004 0.108 0.000
		DHA	56	0.246	0.012	0.233			
		DHA+ARA	59	0.186	0.014	0.169			

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Table 9  
Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	22:4n6	Control	53	0.484	0.048	0.390	0.093		
		DHA	56	0.489	0.061	0.426			
		DHA+ARA	59	0.496	0.027	0.487			
Study Form Termination	24:1	Control	53	0.127	0.039	0.062	0.303		
		DHA	56	0.143	0.036	0.086			
		DHA+ARA	59	0.177	0.040	0.089			
Study Form Termination	22:5n6	Control	53	0.181	0.013	0.163	0.006	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.005 0.895 0.006
		DHA	56	0.145	0.011	0.133			
		DHA+ARA	59	0.172	0.009	0.165			
Study Form Termination	22:4n3	Control	53	0.001	0.001	0.000	0.359		
		DHA	56	0.001	0.001	0.000			
		DHA+ARA	59	0.003	0.002	0.000			
Study Form Termination	22:5n3	Control	53	0.306	0.019	0.289	0.221		
		DHA	56	0.293	0.026	0.260			
		DHA+ARA	59	0.265	0.013	0.255			
Study Form Termination	22:6n3	Control	53	0.895	0.072	0.812	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.000 0.000 0.141
		DHA	56	1.380	0.063	1.352			
		DHA+ARA	59	1.244	0.049	1.259			

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Table 9

Red Blood Cell Phosphatidylcholine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	12:0	Control	37	0.032	0.005	0.026	0.729		
		DHA	32	0.028	0.006	0.016			
		DHA+ARA	38	0.026	0.004	0.021			
		HM	56	0.059	0.016	0.020			
48 Weeks PCA	14:0	Control	37	0.402	0.039	0.331	0.943		
		DHA	32	0.353	0.032	0.324			
		DHA+ARA	38	0.353	0.024	0.328			
		HM	56	0.381	0.026	0.335			
48 Weeks PCA	14:1	Control	37	0.025	0.006	0.013	0.448		
		DHA	32	0.026	0.007	0.011			
		DHA+ARA	38	0.026	0.006	0.015			
		HM	56	0.024	0.003	0.020			
48 Weeks PCA	16:0	Control	37	34.627	0.577	34.319	0.000	Control vs DHA	0.527
		DHA	32	35.272	0.689	34.473		Control vs DHA+ARA	0.593
		DHA+ARA	38	34.802	0.506	34.165		HM vs DHA	0.000
		HM	56	33.037	0.506	32.228		HM vs DHA+ARA	0.000
48 Weeks PCA	16:1	Control	37	0.435	0.043	0.338	0.000	Control vs HM	0.000
		DHA	32	0.380	0.023	0.352		DHA vs DHA+ARA	0.524
		DHA+ARA	38	0.395	0.024	0.368		HM vs DHA	0.467
		HM	56	0.507	0.020	0.473		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.183

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:0	Control	37	13.016	0.313	12.759	0.000	Control vs DHA	0.760
		DHA	32	12.944	0.249	12.786		Control vs DHA+ARA	0.889
		DHA+ARA	38	12.804	0.235	12.793		HM vs DHA	0.000
		HM	56	14.583	0.287	14.729		HM vs DHA+ARA	0.000
48 Weeks PCA	18:1	Control	37	17.894	0.453	18.636	0.256	Control vs HM	0.000
		DHA	32	17.766	0.429	18.492		DHA vs DHA+ARA	0.661
		DHA+ARA	38	17.850	0.289	18.227			
		HM	56	18.662	0.305	18.727			
48 Weeks PCA	18:2	Control	37	23.469	0.518	23.552	0.000	Control vs DHA	0.840
		DHA	32	23.538	0.516	23.717		Control vs DHA+ARA	0.527
		DHA+ARA	38	23.738	0.422	23.839		HM vs DHA	0.000
		HM	56	18.650	0.344	18.482		HM vs DHA+ARA	0.000
48 Weeks PCA	18:3n6	Control	37	0.071	0.008	0.061	0.002	Control vs DHA	0.950
		DHA	32	0.069	0.005	0.067		Control vs DHA+ARA	0.774
		DHA+ARA	38	0.069	0.006	0.062		HM vs DHA	0.004
		HM	56	0.042	0.004	0.039		HM vs DHA+ARA	0.001
48 Weeks PCA	20:0	Control	37	0.348	0.075	0.197	0.785	Control vs HM	0.003
		DHA	32	0.339	0.061	0.206		DHA vs DHA+ARA	0.831
		DHA+ARA	38	0.304	0.061	0.172			
		HM	56	0.409	0.044	0.215			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:3n3	Control	37	0.222	0.019	0.182	0.001	Control vs DHA	0.812
		DHA	32	0.211	0.015	0.182		Control vs DHA+ARA	0.918
		DHA+ARA	38	0.203	0.010	0.190		HM vs DHA	0.001
		HM	56	0.182	0.022	0.120		HM vs DHA+ARA	0.002
								Control vs HM	0.001
								DHA vs DHA+ARA	0.737
48 Weeks PCA	20:1	Control	37	0.418	0.019	0.420	0.000	Control vs DHA	0.579
		DHA	32	0.406	0.025	0.435		Control vs DHA+ARA	0.588
		DHA+ARA	38	0.382	0.016	0.375		HM vs DHA	0.001
		HM	56	0.311	0.014	0.309		HM vs DHA+ARA	0.001
								Control vs HM	0.000
								DHA vs DHA+ARA	0.974
48 Weeks PCA	18:4	Control	37	0.018	0.005	0.000	0.010	Control vs DHA	0.822
		DHA	32	0.016	0.004	0.000		Control vs DHA+ARA	0.161
		DHA+ARA	38	0.007	0.002	0.000		HM vs DHA	0.039
		HM	56	0.024	0.004	0.015		HM vs DHA+ARA	0.001
								Control vs HM	0.054
								DHA vs DHA+ARA	0.262
48 Weeks PCA	20:2n6	Control	37	0.543	0.023	0.537	0.629	Control vs DHA	
		DHA	32	0.557	0.032	0.543		Control vs DHA+ARA	
		DHA+ARA	38	0.636	0.053	0.550		HM vs DHA	
		HM	56	0.560	0.014	0.531		HM vs DHA+ARA	
48 Weeks PCA	20:3n6	Control	37	1.709	0.086	1.741	0.000	Control vs DHA	0.610
		DHA	32	1.702	0.073	1.684		Control vs DHA+ARA	0.735
		DHA+ARA	38	1.844	0.090	1.717		HM vs DHA	0.000
		HM	56	2.265	0.086	2.166		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.405

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	20:4n6	Control	37	4.738	0.255	4.736	0.000	Control vs DHA	0.508
		DHA	32	4.475	0.196	4.499		Control vs DHA+ARA	0.805
		DHA+ARA	38	4.550	0.185	4.746		HM vs DHA	0.000
		HM	56	7.408	0.250	7.666		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.672
48 Weeks PCA	22:1	Control	37	0.166	0.036	0.131	0.664		
		DHA	32	0.116	0.014	0.118			
		DHA+ARA	38	0.131	0.024	0.105			
		HM	56	0.160	0.030	0.104			
48 Weeks PCA	20:5n3	Control	37	0.102	0.015	0.077	0.000	Control vs DHA	0.633
		DHA	32	0.084	0.006	0.083		Control vs DHA+ARA	0.086
		DHA+ARA	38	0.099	0.009	0.078		HM vs DHA	0.000
		HM	56	0.138	0.009	0.123		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.239
48 Weeks PCA	22:4n6	Control	37	0.426	0.059	0.373	0.244		
		DHA	32	0.382	0.029	0.417			
		DHA+ARA	38	0.440	0.054	0.384			
		HM	56	0.406	0.022	0.377			
48 Weeks PCA	24:1	Control	37	0.247	0.070	0.112	0.000	Control vs DHA	0.337
		DHA	32	0.210	0.062	0.116		Control vs DHA+ARA	0.247
		DHA+ARA	38	0.179	0.055	0.108		HM vs DHA	0.000
		HM	56	0.115	0.020	0.079		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.878

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	22:5n6	Control	37	0.210	0.016	0.212	0.000	Control vs DHA	0.505
		DHA	32	0.189	0.012	0.186		Control vs DHA+ARA	0.647
		DHA+ARA	38	0.231	0.022	0.198		HM vs DHA	0.000
		HM	56	0.264	0.016	0.265		HM vs DHA+ARA	0.001
48 Weeks PCA	22:4n3	Control	37	0.000	0.000	0.000	1.000	Control vs HM	0.000
		DHA	32	0.000	0.000	0.000		DHA vs DHA+ARA	0.270
		DHA+ARA	38	0.000	0.000	0.000			
		HM	56	0.000	0.000	0.000			
48 Weeks PCA	22:5n3	Control	37	0.286	0.029	0.260	0.000	Control vs DHA	0.598
		DHA	32	0.253	0.017	0.251		Control vs DHA+ARA	0.759
		DHA+ARA	38	0.268	0.026	0.256		HM vs DHA	0.000
		HM	56	0.339	0.018	0.314		HM vs DHA+ARA	0.000
48 Weeks PCA	22:6n3	Control	37	0.595	0.047	0.569	0.000	Control vs HM	0.000
		DHA	32	0.685	0.048	0.676		DHA vs DHA+ARA	0.817
		DHA+ARA	38	0.662	0.043	0.663		Control vs DHA	0.111
		HM	56	1.475	0.081	1.333		Control vs DHA+ARA	0.052
								HM vs DHA	0.000
								HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.776

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	12:0	Control	52	0.069	0.015	0.022	0.546		
		DHA	57	0.075	0.013	0.033			
		DHA+ARA	61	0.063	0.010	0.039			
Study Form Initiation	14:0	Control	52	0.307	0.038	0.220	0.792		
		DHA	57	0.278	0.025	0.206			
		DHA+ARA	61	0.277	0.021	0.246			
Study Form Initiation	14:1	Control	52	0.080	0.015	0.032	0.181		
		DHA	57	0.061	0.012	0.028			
		DHA+ARA	61	0.062	0.009	0.050			
Study Form Initiation	16:0	Control	52	20.021	0.736	17.945	0.967		
		DHA	57	19.847	0.622	19.295			
		DHA+ARA	61	19.796	0.451	19.035			
Study Form Initiation	16:1	Control	52	0.731	0.035	0.698	0.337		
		DHA	57	0.769	0.034	0.746			
		DHA+ARA	61	0.836	0.035	0.837			
Study Form Initiation	18:0	Control	52	8.857	0.329	8.469	0.142		
		DHA	57	8.434	0.227	8.308			
		DHA+ARA	61	8.201	0.215	7.904			
Study Form Initiation	18:1	Control	52	16.450	0.301	16.698	0.412		
		DHA	57	16.208	0.326	16.308			
		DHA+ARA	61	16.415	0.375	16.001			
Study Form Initiation	18:2	Control	52	6.615	0.253	6.682	0.773		
		DHA	57	6.336	0.280	6.346			
		DHA+ARA	61	6.175	0.294	5.682			
Study Form Initiation	18:3n6	Control	52	0.165	0.018	0.145	0.040	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.373 0.013 0.101
		DHA	57	0.190	0.019	0.152			
		DHA+ARA	61	0.192	0.016	0.169			

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Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	20:0	Control	52	0.372	0.043	0.291	0.151		
		DHA	57	0.314	0.030	0.244			
		DHA+ARA	61	0.259	0.024	0.186			
Study Form Initiation	18:3n3	Control	52	0.305	0.023	0.261	0.641		
		DHA	57	0.269	0.018	0.249			
		DHA+ARA	61	0.257	0.016	0.225			
Study Form Initiation	20:1	Control	52	0.573	0.036	0.517	0.395		
		DHA	57	0.615	0.034	0.555			
		DHA+ARA	61	0.571	0.027	0.544			
Study Form Initiation	18:4	Control	52	0.025	0.005	0.000	0.371		
		DHA	57	0.031	0.004	0.025			
		DHA+ARA	61	0.030	0.007	0.021			
Study Form Initiation	20:2n6	Control	52	0.479	0.023	0.480	0.706		
		DHA	57	0.463	0.024	0.437			
		DHA+ARA	61	0.443	0.028	0.427			
Study Form Initiation	20:3n6	Control	52	1.843	0.072	1.829	0.099		
		DHA	57	1.965	0.077	1.820			
		DHA+ARA	61	1.973	0.064	1.911			
Study Form Initiation	20:4n6	Control	52	25.817	0.618	26.820	0.353		
		DHA	57	26.475	0.611	27.376			
		DHA+ARA	61	26.747	0.645	27.708			
Study Form Initiation	22:1	Control	52	0.150	0.017	0.138	0.572		
		DHA	57	0.167	0.015	0.151			
		DHA+ARA	61	0.168	0.017	0.141			
Study Form Initiation	20:5n3	Control	52	0.378	0.024	0.357	0.997		
		DHA	57	0.384	0.024	0.370			
		DHA+ARA	61	0.366	0.022	0.335			

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Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	22:4n6	Control	52	7.290	0.182	7.402	0.875		
		DHA	57	7.431	0.186	7.638			
		DHA+ARA	61	7.456	0.167	7.270			
Study Form Initiation	24:1	Control	52	0.100	0.028	0.041	0.068		
		DHA	57	0.059	0.009	0.031			
		DHA+ARA	61	0.072	0.010	0.047			
Study Form Initiation	22:5n6	Control	52	1.757	0.083	1.782	0.555		
		DHA	57	1.809	0.070	1.857			
		DHA+ARA	61	1.851	0.075	1.775			
Study Form Initiation	22:4n3	Control	52	0.001	0.001	0.000	0.257		
		DHA	57	0.001	0.001	0.000			
		DHA+ARA	61	0.005	0.002	0.000			
Study Form Initiation	22:5n3	Control	52	1.496	0.109	1.308	0.195		
		DHA	57	1.375	0.109	0.988			
		DHA+ARA	61	1.380	0.097	1.041			
Study Form Initiation	22:6n3	Control	52	6.119	0.200	6.381	0.375		
		DHA	57	6.444	0.185	6.468			
		DHA+ARA	61	6.407	0.220	6.579			

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	12:0	Control	53	0.093	0.018	0.033	0.630		
		DHA	55	0.093	0.019	0.036			
		DHA+ARA	58	0.067	0.012	0.035			
Study Form Termination	14:0	Control	53	0.360	0.031	0.279	0.782		
		DHA	55	0.380	0.039	0.265			
		DHA+ARA	58	0.348	0.030	0.256			
Study Form Termination	14:1	Control	53	0.086	0.020	0.041	0.592		
		DHA	55	0.066	0.013	0.000			
		DHA+ARA	58	0.066	0.011	0.043			
Study Form Termination	16:0	Control	53	19.326	0.673	17.617	0.560		
		DHA	55	19.062	0.614	17.556			
		DHA+ARA	58	18.357	0.467	17.568			
Study Form Termination	16:1	Control	53	0.511	0.034	0.476	0.604		
		DHA	55	0.579	0.045	0.509			
		DHA+ARA	58	0.618	0.049	0.555			
Study Form Termination	18:0	Control	53	9.614	0.266	9.406	0.024	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.130 0.006 0.219
		DHA	55	9.173	0.208	8.818			
		DHA+ARA	58	8.961	0.242	8.697			
Study Form Termination	18:1	Control	53	14.763	0.437	14.695	0.333		
		DHA	55	15.177	0.299	14.927			
		DHA+ARA	58	14.814	0.330	14.499			
Study Form Termination	18:2	Control	53	9.405	0.192	9.359	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.908 0.000 0.000
		DHA	55	9.180	0.207	9.188			
		DHA+ARA	58	7.756	0.141	7.586			
Study Form Termination	18:3n6	Control	53	0.169	0.012	0.163	0.160		
		DHA	55	0.187	0.017	0.157			
		DHA+ARA	58	0.198	0.018	0.161			

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Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	20:0	Control	53	0.404	0.044	0.278	0.146		
		DHA	55	0.336	0.037	0.208			
		DHA+ARA	58	0.288	0.029	0.208			
Study Form Termination	18:3n3	Control	53	0.382	0.017	0.364	0.134		
		DHA	55	0.368	0.016	0.354			
		DHA+ARA	58	0.329	0.015	0.305			
Study Form Termination	20:1	Control	53	0.553	0.029	0.526	0.164		
		DHA	55	0.579	0.028	0.537			
		DHA+ARA	58	0.507	0.025	0.483			
Study Form Termination	18:4	Control	53	0.042	0.010	0.018	0.108		
		DHA	55	0.026	0.005	0.019			
		DHA+ARA	58	0.022	0.004	0.000			
Study Form Termination	20:2n6	Control	53	0.754	0.029	0.765	0.068		
		DHA	55	0.774	0.030	0.750			
		DHA+ARA	58	0.654	0.026	0.663			
Study Form Termination	20:3n6	Control	53	2.253	0.111	2.073	0.203		
		DHA	55	2.295	0.094	2.206			
		DHA+ARA	58	2.066	0.073	1.992			
Study Form Termination	20:4n6	Control	53	24.279	0.527	25.132	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.119 0.000 0.000
		DHA	55	23.464	0.520	24.038			
		DHA+ARA	58	26.760	0.437	27.372			
Study Form Termination	22:1	Control	53	0.149	0.019	0.122	0.229		
		DHA	55	0.176	0.016	0.169			
		DHA+ARA	58	0.146	0.012	0.130			
Study Form Termination	20:5n3	Control	53	0.519	0.020	0.493	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.286 0.000 0.000
		DHA	55	0.563	0.025	0.575			
		DHA+ARA	58	0.411	0.015	0.415			

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Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	22:4n6	Control	53	7.309	0.208	7.656	0.007	Control vs DHA	0.025
		DHA	55	7.135	0.154	6.885		Control vs DHA+ARA	0.461
		DHA+ARA	58	7.592	0.155	7.635		DHA vs DHA+ARA	0.002
Study Form Termination	24:1	Control	53	0.092	0.023	0.038	0.294		
		DHA	55	0.056	0.009	0.042			
		DHA+ARA	58	0.062	0.008	0.041			
Study Form Termination	22:5n6	Control	53	1.444	0.064	1.423	0.010	Control vs DHA	0.003
		DHA	55	1.231	0.034	1.213		Control vs DHA+ARA	0.255
		DHA+ARA	58	1.347	0.040	1.330		DHA vs DHA+ARA	0.050
Study Form Termination	22:4n3	Control	53	0.000	0.000	0.000	0.137		
		DHA	55	0.004	0.002	0.000			
		DHA+ARA	58	0.004	0.002	0.000			
Study Form Termination	22:5n3	Control	53	2.694	0.110	2.839	0.003	Control vs DHA	0.004
		DHA	55	2.334	0.091	2.400		Control vs DHA+ARA	0.002
		DHA+ARA	58	2.237	0.069	2.269		DHA vs DHA+ARA	0.943
Study Form Termination	22:6n3	Control	53	4.798	0.151	4.815	0.000	Control vs DHA	0.000
		DHA	55	6.762	0.183	7.043		Control vs DHA+ARA	0.000
		DHA+ARA	58	6.389	0.150	6.498		DHA vs DHA+ARA	0.027

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	12:0	Control	37	0.053	0.019	0.024	0.587		
		DHA	32	0.054	0.016	0.019			
		DHA+ARA	38	0.047	0.014	0.018			
		HM	56	0.045	0.011	0.023			
48 Weeks PCA	14:0	Control	37	0.243	0.030	0.169	0.598		
		DHA	32	0.251	0.041	0.162			
		DHA+ARA	38	0.235	0.025	0.188			
		HM	56	0.230	0.016	0.210			
48 Weeks PCA	14:1	Control	37	0.080	0.017	0.037	0.092		
		DHA	32	0.055	0.017	0.000			
		DHA+ARA	38	0.078	0.019	0.044			
		HM	56	0.053	0.011	0.021			
48 Weeks PCA	16:0	Control	37	17.319	0.595	16.314	0.177		
		DHA	32	17.101	0.729	15.692			
		DHA+ARA	38	17.225	0.538	16.997			
		HM	56	18.138	0.395	17.607			
48 Weeks PCA	16:1	Control	37	0.440	0.050	0.349	0.000	Control vs DHA	0.601
		DHA	32	0.390	0.035	0.336		Control vs DHA+ARA	0.524
		DHA+ARA	38	0.390	0.022	0.376		HM vs DHA	0.000
		HM	56	0.596	0.027	0.562		HM vs DHA+ARA	0.000
								Control vs HM	0.001
								DHA vs DHA+ARA	0.928

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Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:0	Control	37	7.935	0.327	7.174	0.000	Control vs DHA	0.347
		DHA	32	7.962	0.293	7.552		Control vs DHA+ARA	0.483
		DHA+ARA	38	7.443	0.270	7.173		HM vs DHA	0.020
		HM	56	8.754	0.230	8.409		HM vs DHA+ARA	0.000
								Control vs HM	0.001
								DHA vs DHA+ARA	0.108
48 Weeks PCA	18:1	Control	37	19.438	0.368	19.410	0.038	Control vs DHA	0.401
		DHA	32	19.066	0.421	19.534		Control vs DHA+ARA	0.234
		DHA+ARA	38	19.302	0.332	19.433		HM vs DHA	0.067
		HM	56	18.469	0.278	18.141		HM vs DHA+ARA	0.118
								Control vs HM	0.005
								DHA vs DHA+ARA	0.758
48 Weeks PCA	18:2	Control	37	9.328	0.261	9.267	0.000	Control vs DHA	0.024
		DHA	32	8.867	0.210	8.696		Control vs DHA+ARA	0.187
		DHA+ARA	38	9.257	0.216	8.840		HM vs DHA	0.000
		HM	56	6.291	0.193	6.027		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.318
48 Weeks PCA	18:3n6	Control	37	0.198	0.020	0.182	0.050	Control vs DHA	0.879
		DHA	32	0.219	0.031	0.171		Control vs DHA+ARA	0.590
		DHA+ARA	38	0.188	0.021	0.158		HM vs DHA	0.029
		HM	56	0.129	0.012	0.112		HM vs DHA+ARA	0.061
								Control vs HM	0.014
								DHA vs DHA+ARA	0.714
48 Weeks PCA	20:0	Control	37	0.263	0.058	0.146	0.728		
		DHA	32	0.262	0.042	0.145			
		DHA+ARA	38	0.212	0.037	0.125			
		HM	56	0.295	0.031	0.240			

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:3n3	Control	37	0.291	0.025	0.225	0.001	Control vs DHA	0.559
		DHA	32	0.270	0.017	0.262		Control vs DHA+ARA	0.848
		DHA+ARA	38	0.265	0.015	0.245		HM vs DHA	0.008
		HM	56	0.226	0.020	0.169		HM vs DHA+ARA	0.002
								Control vs HM	0.001
								DHA vs DHA+ARA	0.689
48 Weeks PCA	20:1	Control	37	0.715	0.031	0.648	0.000	Control vs DHA	0.339
		DHA	32	0.772	0.032	0.782		Control vs DHA+ARA	0.512
		DHA+ARA	38	0.936	0.188	0.738		HM vs DHA	0.000
		HM	56	0.533	0.024	0.492		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.115
48 Weeks PCA	18:4	Control	37	0.017	0.005	0.003	0.057		
		DHA	32	0.017	0.005	0.000			
		DHA+ARA	38	0.023	0.006	0.000			
		HM	56	0.027	0.004	0.019			
48 Weeks PCA	20:2n6	Control	37	0.672	0.035	0.698	0.000	Control vs DHA	0.543
		DHA	32	0.668	0.026	0.684		Control vs DHA+ARA	0.532
		DHA+ARA	38	0.715	0.032	0.689		HM vs DHA	0.000
		HM	56	0.444	0.016	0.412		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.995
48 Weeks PCA	20:3n6	Control	37	2.138	0.099	1.999	0.012	Control vs DHA	0.896
		DHA	32	2.165	0.100	2.045		Control vs DHA+ARA	0.935
		DHA+ARA	38	2.172	0.114	2.132		HM vs DHA	0.015
		HM	56	1.715	0.053	1.637		HM vs DHA+ARA	0.006
								Control vs HM	0.007
								DHA vs DHA+ARA	0.835

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Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	20:4n6	Control	37	24.508	0.536	24.774	0.950		
		DHA	32	24.428	0.491	25.206			
		DHA+ARA	38	24.788	0.429	25.122			
		HM	56	24.625	0.384	25.189			
48 Weeks PCA	22:1	Control	37	0.168	0.016	0.172	0.121		
		DHA	32	0.189	0.022	0.188			
		DHA+ARA	38	0.154	0.022	0.133			
		HM	56	0.148	0.013	0.134			
48 Weeks PCA	20:5n3	Control	37	0.382	0.026	0.368	0.497		
		DHA	32	0.369	0.015	0.377			
		DHA+ARA	38	0.347	0.011	0.347			
		HM	56	0.384	0.016	0.360			
48 Weeks PCA	22:4n6	Control	37	8.580	0.267	8.761	0.001	Control vs DHA	0.612
		DHA	32	8.791	0.250	9.132		Control vs DHA+ARA	0.416
		DHA+ARA	38	8.576	0.188	8.472		HM vs DHA	0.000
		HM	56	7.727	0.203	7.618		HM vs DHA+ARA	0.013
48 Weeks PCA	24:1	Control	37	0.067	0.016	0.035	0.943	Control vs HM	0.001
		DHA	32	0.049	0.009	0.034		DHA vs DHA+ARA	0.199
		DHA+ARA	38	0.046	0.008	0.036			
		HM	56	0.062	0.016	0.027			

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	22:5n6	Control	37	1.401	0.066	1.411	0.000	Control vs DHA	0.977
		DHA	32	1.353	0.057	1.414		Control vs DHA+ARA	0.997
		DHA+ARA	38	1.364	0.054	1.359		HM vs DHA	0.000
		HM	56	1.883	0.056	1.889		HM vs DHA+ARA	0.000
48 Weeks PCA	22:4n3	Control	37	0.000	0.000	0.000	1.000	Control vs HM	0.000
		DHA	32	0.000	0.000	0.000		DHA vs DHA+ARA	0.975
		DHA+ARA	38	0.000	0.000	0.000			
		HM	56	0.001	0.001	0.000			
48 Weeks PCA	22:5n3	Control	37	2.567	0.092	2.681	0.000	Control vs DHA	0.884
		DHA	32	2.561	0.086	2.630		Control vs DHA+ARA	0.148
		DHA+ARA	38	2.436	0.066	2.443		HM vs DHA	0.000
		HM	56	1.942	0.065	1.978		HM vs DHA+ARA	0.000
48 Weeks PCA	22:6n3	Control	37	3.196	0.159	3.013	0.000	Control vs DHA	0.000
		DHA	32	4.143	0.177	4.079		Control vs DHA+ARA	0.000
		DHA+ARA	38	3.801	0.134	3.721		HM vs DHA	0.000
		HM	56	7.283	0.201	7.341		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.281

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Table 11  
Preterm Infant Complications

	Regimen			p-value*
	Control	DHA	DHA+ARA	
Retinopathy of Prematurity Test Results				
Absent	34 (76%)	44 (76%)	41 (79%)	0.91
I	8 (18%)	11 (19%)	6 (12%)	
II	2 (4%)	2 (3%)	4 (8%)	
III	1 (2%)	1 (2%)		
Present, but not graded			1 (2%)	
Ultrasound Examination for Intraventricular Hemorrhage				
None	47 (81%)	52 (84%)	49 (80%)	0.78
Stage 1	6 (10%)	9 (15%)	7 (11%)	
Stage 2	3 (5%)		2 (3%)	
Stage 3	1 (2%)		1 (2%)	
Stage 4	1 (2%)		2 (3%)	
Questionable		1 (2%)		
Posthemorrhagic Hydrocephalus developed?				
No	61 (98%)	65 (98%)	64 (97%)	1.00
Yes	1 (2%)	1 (2%)	2 (3%)	

\*The statistical test was based on a dichotomous response: present or absent.

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Table 12

## Serious Adverse Events Reported During Study Formula Phase

Event	Regimen			p-value
	Control	DHA	DHA+ARA	
Any Event	4 (6%)	3 (5%)	4 (6%)	0.93
Other Respiratory Conditions of Fetus and Newborn	2 (3%)	0	0	0.10
Other Infection Specific to the Perinatal Period	1 (2%)	0	0	0.32
Intraventricular Hemorrhage	0	0	1 (2%)	1.00
Other Specified Perinatal Disorders of Digestive System	0	1 (2%)	0	1.00
Convulsions in Newborn	1 (2%)	0	0	0.32
Feeding Problems in Newborn	0	1 (2%)	1 (2%)	1.00
Hernia	0	0	1 (2%)	1.00
Other	0	1 (2%)	1 (2%)	1.00

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Table 13

## Serious Adverse Events Reported During the Term Formula Phase

Event	Regimen				p-value
	Control	DHA	DHA + ARA	HM	
Any Event	7 (13%)	9 (15%)	9 (15%)	1 (1%)	0.002 C vs D 0.79 C vs D+A 0.79 D vs D+A 1.00 C vs HM 0.006 D vs HM 0.001 D+A vs HM 0.001
Infectious Colitis, Enteritis, and Gastroenteritis	0	0	1 (2%)	0	0.67
Croup	0	0	1 (2%)	0	0.67
Bronchopneumonia, Organism Unspecified	2 (4%)	3 (5%)	6 (10%)	0	0.013 C vs D 1.00 C vs D+A 0.27 D vs D+A 0.49 C vs HM 0.15 D vs HM 0.064 D+A vs HM 0.004
Asthma, Unspecified	1 (2%)	0	0	0	0.21
Esophageal Reflux	0	1 (2%)	2 (3%)	0	0.23
Dyspepsia and Other Stomach Function Disorder	0	0	0	1 (1%)	1.0
Other Respiratory Conditions of Fetus and Newborn	1 (2%)	1 (2%)	3 (5%)	0	0.11
Convulsions	1 (2%)	0	0	0	0.21
Sudden Infant Death Syndrome	1 (2%)	1 (2%)	0	0	0.34
Hernia	2 (4%)	2 (3%)	0	0	0.11
Other	0	3 (5%)	2 (3%)	0	0.063

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9698-0301	Weight (g) Age (weeks pca)	1120 30.3	1240 31.3	1360 32.1	1590 33.1	1870 34.1					27.7			
Male	Control	9698-0304	Weight (g) Age (weeks pca)	1450 32.6	1630 33.4	1940 34.7	2180 35.4						36.1	3731 40.3	5752 48.3	6816 56.6
Male	Control	9699-0302	Weight (g) Age (weeks pca)	958.0 30.7	1108 31.7	1251 32.7	1378 33.7	1659 34.7					23.9	3064 39.9	4993 48.0	6553 57.9
Male	Control	9699-0306	Weight (g) Age (weeks pca)	1185 31.0	1261 32.0	1437 33.0	1647 34.0	1933 35.0					26.9	3575 40.3	4936 48.3	6014 57.1
Male	Control	9699-0308	Weight (g) Age (weeks pca)	1600 34.4	1840 35.4	2752 38.3							43.3	3688 40.3	5504 48.3	6922 57.3
Male	Control	9700-0301	Weight (g) Age (weeks pca)	1810 32.1	1855 32.6	2075 33.4	2330 34.4	2595 35.4	3120 37.4				36.2	3745 40.1	5080 47.6	6610 56.7
Male	Control	9701-0303	Weight (g) Age (weeks pca)	1181 32.4	1298 33.4	1494 34.4	1785 35.4	2012 36.3					31.5	3070 41.6	3895 48.6	4965 57.6
Male	Control	9701-0304	Weight (g) Age (weeks pca)	1412 31.9	1566 32.9	1851 33.7	2117 34.7	2318 35.9					34.1	3070 39.9	5445 48.3	7135 56.9
Male	Control	9702-0302	Weight (g) Age (weeks pca)	1480 31.0	1775 32.1	2045 33.0	2240 34.0	2340 34.6	2570 35.6				33.8	3590 40.1	4840 48.6	6110 58.4
Male	Control	9703-0302	Weight (g) Age (weeks pca)	1785 33.3	2040 34.6	2375 35.6	2685 36.4	2955 37.4					41.7	3620 39.7	5850 48.6	7470 57.3
Male	Control	9703-0304	Weight (g) Age (weeks pca)	1475 31.7	1705 33.0	1920 34.0	2190 34.9	2425 35.7					34.2	3170 40.1	5240 47.7	6970 57.1
Male	Control	9703-0308	Weight (g) Age (weeks pca)	1140 31.7	1230 32.6	1445 33.7	1665 34.7	1945 35.7					28.9	2520 39.7	4010 48.4	5030 56.9
Male	Control	9704-0303	Weight (g) Age (weeks pca)	975.0 32.3	1205 33.4	1270 34.4	1450 35.4	1665 36.3	1760 37.3	2045 38.3			24.4	2150 39.3	3700 48.3	4950 57.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9704-0305	Weight (g) Age (weeks pca)	1315 30.9	1475 32.0	1640 33.0	1860 34.1						23.7			
Male	Control	9705-0302	Weight (g) Age (weeks pca)	1280 33.0	1389 34.0	1588 35.0	1786 36.0	2240 37.4					30.9	2540 39.6	4936 47.4	5646 56.4
Male	Control	9705-0304	Weight (g) Age (weeks pca)	1270 31.3	1280 32.3	1570 33.3	1810 34.6						25.3	3291 39.7	5816 47.7	7490 56.7
Male	Control	9706-0302	Weight (g) Age (weeks pca)	1645 35.7	1865 36.6	2130 37.7	2435 38.7						37.1	2800 40.1	4660 48.7	6170 56.7
Male	Control	9706-0303	Weight (g) Age (weeks pca)	1875 33.7	1984 34.7	2135 35.6	2185 36.4	2465 37.3					22.2	3050 41.0	4550 48.6	6675 56.9
Male	Control	9706-0308	Weight (g) Age (weeks pca)	1655 32.9	1734 33.1	2005 34.0	2495 35.4						46.9	3835 40.6	5155 48.0	6090 56.3
Male	Control	9707-0302	Weight (g) Age (weeks pca)	1544 31.6	1820 32.9	2215 34.4	2450 35.4	2460 35.7					32.8	2930 40.1	3795 47.7	5185 56.6
Male	Control	9707-0303	Weight (g) Age (weeks pca)	1415 33.1	1600 34.1	1850 35.1	2195 36.6	2310 37.1					32.7	2530 39.7	4235 47.7	6530 57.1
Male	Control	9707-0309	Weight (g) Age (weeks pca)	1046 30.9	1442 32.7	1644 33.7	1910 34.9						30.7	2965 39.9	4465 48.0	
Male	Control	9708-0303	Weight (g) Age (weeks pca)	1730 32.7	1960 33.7	2205 34.7	2520 35.7						37.4	3680 40.1	5470 48.1	7330 57.0
Male	Control	9709-0302	Weight (g) Age (weeks pca)	1090 29.9	1440 31.7	1660 32.7	1910 33.7	2040 34.3					30.8	3845 39.9	5700 48.0	6775 56.7
Male	Control	9712-0301*	Weight (g) Age (weeks pca)	1245 31.6	1221 31.7	1245 31.9	1291 32.0	1294 32.1	1330 32.3	1369 32.4	1402 32.6	1433 32.7	26.1			
Male	Control	9712-0302	Weight (g) Age (weeks pca)	1292 33.1	1345 34.1	1456 35.1	1670 36.1	1835 37.1	1985 38.1				21.0	2160 40.1	3300 47.7	3980 57.3

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9743-0301	Weight (g) Age (weeks pca)	1520 34.1	1570 35.0	1670 36.0	1720 37.1						10.0	2260 41.0	4535 50.0	
Male	Control	9746-0301	Weight (g) Age (weeks pca)	2065 37.6	2465 38.9	2760 39.7	3085 40.6	3085 40.6					48.9	3085 40.6	4795 47.6	6695 57.6
Male	DIHA	9698-0302	Weight (g) Age (weeks pca)	1640 35.1	1860 36.1	3170 39.9							47.5	3170 39.9	5206 47.9	7036 57.1
Male	DIHA	9698-0306	Weight (g) Age (weeks pca)	1620 35.1	1830 36.3	2090 37.3	2575 40.0						28.3	2575 40.0	4334 48.0	6022 57.0
Male	DIHA	9699-0301	Weight (g) Age (weeks pca)	1018 31.3	1207 32.3	1360 33.3	1617 34.3						27.9	3121 39.9	5192 48.0	6752 57.9
Male	DIHA	9699-0303	Weight (g) Age (weeks pca)	1258 32.4	1435 33.4	1631 34.4	1882 35.4	2724 36.4					48.3	2724 40.1	4341 48.1	5674 57.0
Male	DIHA	9699-0307	Weight (g) Age (weeks pca)	1182 34.7	1358 35.7	1484 36.7	1666 37.7						22.5	1986 40.0	3206 48.0	4511 57.0
Male	DIHA	9700-0303	Weight (g) Age (weeks pca)	1830 33.9	1980 34.4	2450 35.9	3045 37.7						45.4	3585 39.6	5420 47.4	7035 56.7
Male	DIHA	9701-0301	Weight (g) Age (weeks pca)	1098 29.6	1234 30.6	1365 31.6	1689 33.4	1902 34.6	2019 35.6	2104 36.4	2276 37.4	2288 38.6	20.4	2805 40.4	3405 47.6	4660 57.0
Male	DIHA	9701-0305	Weight (g) Age (weeks pca)	1621 31.7	1829 33.1	1880 33.7	2253 34.7	2582 35.7					34.7	3660 39.7		
Male	DIHA	9703-0303	Weight (g) Age (weeks pca)	1775 33.3	2030 34.1	2285 35.1	2595 36.0	2780 37.1					38.2	3080 39.9	3940 48.0	5260 56.9
Male	DIHA	9703-0306	Weight (g) Age (weeks pca)	1725 33.4	1870 34.0	2180 35.0							41.7			
Male	DIHA	9703-0307	Weight (g) Age (weeks pca)	1525 32.7	1725 33.7	2020 34.9	2390 36.0						37.6	3120 40.7	4410 47.9	5600 56.9

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DHA	9704-0304	Weight (g) Age (weeks pca)	1380 32.1	1570 33.1	1730 34.1	1960 35.0	2140 35.9					29.3	2880 40.3	3900 48.3	4300 57.3
Male	DHA	9704-0306	Weight (g) Age (weeks pca)	1320 30.7	1370 31.7	1550 32.7	1760 33.7	2020 34.7	2170 35.9				25.6		3750 48.0	4800 57.0
Male	DHA	9705-0303	Weight (g) Age (weeks pca)	1380 33.0	1446 34.0	1616 35.0	1843 36.0	2330 37.4					30.8	2370 39.6	4170 47.4	5787 56.4
Male	DHA	9705-0305	Weight (g) Age (weeks pca)	1490 31.1	1770 32.1	1980 33.1	2240 34.0						36.7	3291 39.6		
Male	DHA	9706-0304	Weight (g) Age (weeks pca)	1490 33.0	1655 33.7	1915 34.7	2260 36.0						36.8	3335 40.0	5265 48.1	6900 57.3
Male	DHA	9706-0306	Weight (g) Age (weeks pca)	1604 34.4	1908 35.4	2160 36.3							42.8	3310 41.4	4205 47.6	5600 56.9
Male	DHA	9707-0001	Weight (g) Age (weeks pca)	1305 31.0	1429 32.0								17.7			
Male	DHA	9707-0304	Weight (g) Age (weeks pca)	1555 32.0	1740 33.0	1990 34.0	2400 35.4	2570 36.0					36.9	3280 39.9	5115 48.0	6755 57.6
Male	DHA	9707-0306	Weight (g) Age (weeks pca)	1728 36.1	2040 37.3	2260 38.1	3050 40.6	3050 40.6					43.2	3050 40.6	5100 48.6	7150 57.6
Male	DHA	9707-0307*	Weight (g) Age (weeks pca)	1649 32.4	1675 32.6	1699 32.7	1732 32.9	1778 33.0	1811 33.1	1858 33.3	1882 33.4	1938 33.6	39.6			
Male	DHA	9707-1308	Weight (g) Age (weeks pca)	1780 34.4	2045 35.7	3004 39.3	3004 39.3						36.7	3004 39.3	4420 47.3	6090 57.7
Male	DHA	9707-2308	Weight (g) Age (weeks pca)	1651 34.4	1923 35.7	2850 39.3	2850 39.3						35.8	2850 39.3	4375 47.3	5930 57.7
Male	DHA	9708-0302	Weight (g) Age (weeks pca)	1485 33.3	1740 34.3	2500 37.0							39.2	3873 42.9		6256 57.3

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DIIA	9709-0301	Weight (g) Age (weeks pca)	1490 32.4	1740 33.4	2000 34.4	2400 35.4	2800 36.7					44.4	3150 39.4	5080 47.4	6750 56.4
Male	DIIA	9709-0304	Weight (g) Age (weeks pca)	1470 34.4	1520 35.4								7.1			
Male	DIIA	9712-0304	Weight (g) Age (weeks pca)	1545 33.0	1800 34.0	1985 35.0	2160 36.0	2550 37.6					30.5	3160 40.3	5200 48.1	7300 57.1
Male	DIIA	9712-0306	Weight (g) Age (weeks pca)	1240 31.5	1435 32.5	1695 33.5	1945 34.5						33.9	3040 39.6	4680 48.6	5860 57.6
Male	DIIA	9743-0303	Weight (g) Age (weeks pca)	1700 32.9	1810 33.9	2100 34.9	2300 35.7						31.1	3100 40.6	5500 48.6	
Male	DIIA	9743-0304	Weight (g) Age (weeks pca)	1530 32.3	1880 34.0	2160 35.0	2375 36.0	2440 36.4					32.2	3628 38.1	5840 50.6	
Male	DIIA+ARA	9698-0305	Weight (g) Age (weeks pca)	1120 30.7	1340 32.6	1550 33.6							20.9	2440 37.4	5525 47.6	6646 56.6
Male	DIIA+ARA	9698-0308	Weight (g) Age (weeks pca)	1410 31.1	1690 32.4	1870 33.3	2120 34.3						32.0	3553 40.3	6007 47.6	7937 57.3
Male	DIIA+ARA	9699-0304	Weight (g) Age (weeks pca)	1499 36.1	1689 37.1	1950 38.1	2355 40.3						29.8	2355 40.3	3404 48.0	4993 57.1
Male	DIIA+ARA	9699-0305	Weight (g) Age (weeks pca)	1056 32.0	1134 33.0	1290 34.0	1490 35.7						17.2	2610 40.6	4256 48.7	5050 57.6
Male	DIIA+ARA	9700-0302	Weight (g) Age (weeks pca)	1635 33.9	1880 34.7	2235 35.9	2570 36.9	2735 37.9					40.7	3255 39.7	5540 47.7	7380 56.7
Male	DIIA+ARA	9701-0302	Weight (g) Age (weeks pca)	1442 33.6	1686 34.6	2045 35.6	2835 37.7						48.9	3240 39.7	5055 46.7	6600 56.7
Male	DIIA+ARA	9701-0306	Weight (g) Age (weeks pca)	1587 32.3	2037 33.4	2245 34.4	2460 35.3	2756 36.3	3072 37.3	3228 37.7			41.4	3960 42.3	5200 48.4	

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DHA+ARA	9701-0307	Weight (g) Age (weeks pca)	1397 33.3	1710 34.3	1919 35.1	2932 38.4						42.5	3445 40.6	5930 48.6	7475 57.4
Male	DHA+ARA	9702-0301	Weight (g) Age (weeks pca)	1670 32.0	1865 33.0	2160 34.0	2660 36.0						36.0	3780 40.6	5250 47.6	
Male	DHA+ARA	9702-0303	Weight (g) Age (weeks pca)	1650 32.9	1905 33.9	2660 36.4							40.7	3500 40.0	5160 48.0	6520 56.4
Male	DHA+ARA	9703-0301	Weight (g) Age (weeks pca)	1255 29.4	1460 30.4	1745 31.3	2055 32.3	2415 33.4					42.3	4350 40.4	6020 47.4	6720 56.6
Male	DHA+ARA	9703-0305	Weight (g) Age (weeks pca)	1440 32.0	1635 33.0	1830 34.0	2115 35.0	2390 36.1	2590 36.9				34.1	3170 40.0	4330 47.9	5630 56.7
Male	DHA+ARA	9704-0301	Weight (g) Age (weeks pca)	1110 30.6	1270 31.6	1490 32.4	1740 33.4	2050 34.4					35.1	3220 39.9	5460 47.7	7050 56.7
Male	DHA+ARA	9704-0302	Weight (g) Age (weeks pca)	1080 32.0	1230 33.0	1370 34.0	1520 34.9	1680 36.0	1840 36.9				22.2	2570 40.0	6540 48.1	8050 57.4
Male	DHA+ARA	9705-0301	Weight (g) Age (weeks pca)	1300 32.7	1440 33.7	1620 34.7	1870 35.7						27.0	2979 40.1	4400 48.1	5873 58.0
Male	DHA+ARA	9705-0306	Weight (g) Age (weeks pca)	1320 31.4	1490 32.4	1700 33.4	2020 34.4	2300 35.9					32.7	3631 39.9	5447 47.9	6809 56.9
Male	DHA+ARA	9705-0307	Weight (g) Age (weeks pca)	1480 34.4	1650 35.4	1810 36.1	2240 37.4						36.4	3007 39.9	5589 48.4	6596 56.7
Male	DHA+ARA	9706-0305	Weight (g) Age (weeks pca)	1330 33.9	1455 34.4	1660 35.4	1930 36.6						31.4	2695 39.9	4820 48.1	6225 58.1
Male	DHA+ARA	9706-0307	Weight (g) Age (weeks pca)	1355 31.9	1585 33.0	1825 33.9	2270 35.1						40.0	3585 40.4	5955 49.1	6925 57.6
Male	DHA+ARA	9706-0309	Weight (g) Age (weeks pca)	1620 34.1	1910 35.3	2150 36.0							40.3	3460 40.9	5255 48.7	5775 57.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DHA+ARA	9707-0301	Weight (g) Age (weeks pca)	1553 32.6	1980 34.3	2280 35.3	2720 36.6						41.5	3395 40.1	4950 47.9	6285 56.9
Male	DHA+ARA	9707-0305	Weight (g) Age (weeks pca)	1755 33.9	1990 34.7	2245 35.7	2505 36.7	2770 37.7					37.4			
Male	DHA+ARA	9707-0310	Weight (g) Age (weeks pca)	1620 32.7	1828 33.7	2140 34.7	3195 37.9						44.8	3585 39.7	5170 47.9	6725 56.3
Male	DIHA+ARA	9708-0301	Weight (g) Age (weeks pca)	1640 32.7	1880 33.7	2200 34.7	2420 35.7						38.0	3730 40.1	4835 47.9	6185 57.0
Male	DIHA+ARA	9708-0304	Weight (g) Age (weeks pca)	1680 34.6	2180 35.9								55.6			
Male	DIHA+ARA	9709-0303	Weight (g) Age (weeks pca)	1470 32.6	1810 33.6								48.6			
Male	DIHA+ARA	9709-0305	Weight (g) Age (weeks pca)	1410 34.4	1655 35.4	1900 36.4	2160 37.4						35.6	2630 39.7	4570 47.7	5520 57.1
Male	DHA+ARA	9712-0303	Weight (g) Age (weeks pca)	1180 31.4	1210 32.3	1450 33.4	1590 34.4						20.9	2520 40.4	3500 47.4	5010 56.4
Male	DIHA+ARA	9712-0305	Weight (g) Age (weeks pca)	1325 31.5	1505 32.5	1785 33.5	2010 34.5	2300 35.6					34.1	3030 39.6	4350 48.6	5510 57.6
Male	DIHA+ARA	9723-0301	Weight (g) Age (weeks pca)	1630 33.9	1728 34.9	1961 35.9	2214 36.9						28.4	3104 40.3		5986 58.9
Male	HM	9698-0601												3518 40.0	5497 48.3	6582 56.9
Male	HM	9698-0602												3177 40.0	5220 48.1	6355 57.0
Male	HM	9698-0603												3858 40.0	5447 48.0	6454 57.0

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IIM	9698-0604												4355 40.0	5092 48.0	6383 57.0
Male	IIM	9698-0605												3433 40.0	4979 48.1	6426 57.1
Male	IIM	9699-0501												3915 40.0	6639 48.3	7773 57.4
Male	IIM	9699-0502												3802 40.0	5787 48.4	7178 57.4
Male	IIM	9701-0601												3317 40.0	5555 47.9	7070 56.4
Male	IIM	9701-0602												3487 40.0	5833 47.3	8070 58.3
Male	IIM	9701-0603												3232 40.0	4940 47.4	5855 56.4
Male	IIM	9701-0604												3600 40.0	5215 47.9	6285 56.9
Male	IIM	9701-0605												3402 40.0	5575 47.6	7210 57.6
Male	IIM	9701-0606												3090 40.0	4485 47.7	5445 56.7
Male	IIM	9702-0601												3480 40.0	5780 48.6	6530 56.6
Male	IIM	9702-0602												3165 40.0	5060 48.3	6660 57.1
Male	IIM	9703-0502												2670 40.0	5420 48.3	7220 57.1

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	HM	9703-0503												4100 40.0	6740 47.4	8330 56.4
Male	HM	9703-0504												3435 40.0	6000 48.1	7930 57.1
Male	HM	9704-0502												3285 40.0	5220 48.1	6560 56.6
Male	HM	9704-0503												3400 40.0	5200 48.7	6725 56.9
Male	HM	9705-0601												3200 40.0	5617 48.3	6752 57.3
Male	HM	9705-0602												3860 40.0	6227 48.0	
Male	HM	9706-0601												3152 40.0	5105 49.0	6545 57.0
Male	HM	9706-0602												3557 40.0	5175 47.4	7315 57.7
Male	HM	9706-0603												3192 40.0	5070 47.9	6970 56.7
Male	HM	9706-0604												3461 40.0	4225 48.0	5525 57.1
Male	HM	9706-0605												3870 40.0	6220 48.1	7660 56.4
Male	HM	9706-0606												4315 40.0	5975 48.3	6720 56.6
Male	HM	9707-0601												3263 40.0	4730 48.1	5825 57.0

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IIM	9707-0602												3206 40.0	4515 48.1	6220 57.7
Male	IIM	9707-0603												4256 40.0	6930 48.0	8810 57.0
Male	IIM	9707-0604												3419 40.0	5460 48.0	6130 56.7
Male	IIM	9707-0605												3433 40.0		
Male	IIM	9707-0606												3603 40.0	5825 48.4	
Male	IIM	9707-0607												3569 40.0	5410 47.9	6870 56.9
Male	IIM	9707-0608												3348 40.0	5135 48.0	6370 57.0
Male	IIM	9707-0609												3348 40.0		
Male	IIM	9708-0601												3064 40.0	5220 47.6	6595 56.4
Male	IIM	9708-0602												4085 40.0		
Male	IIM	9708-0603												3319 40.0	5135 48.4	6327 57.1
Male	IIM	9708-0604												3291 40.0		
Male	IIM	9708-0605												3796 40.0		

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IM	9708-0606												4020	4645	5405
														40.0	48.4	57.1
Male	IM	9708-0607												3333	4043	5180
														40.0	47.9	56.7
Male	IM	9709-0505												3400		
														40.0		
Female	Control	9698-0003*	Weight (g)	1020	1050	1070	1080	1080	1060	1080	1070		5.6			
			Age (weeks pca)	31.1	31.3	31.4	31.6	31.7	31.9	32.0	32.1					
Female	Control	9699-0001	Weight (g)	1464	1672	1862	2000	2145					24.1	2610	4369	5220
			Age (weeks pca)	32.7	33.7	34.7	35.7	36.7						39.7	47.9	56.9
Female	Control	9699-0003	Weight (g)	1473	1629	1860	2497						37.3	2780	4596	5816
			Age (weeks pca)	34.0	35.0	36.0	38.0							40.0	48.0	57.0
Female	Control	9701-0003	Weight (g)	1480	1633	1903	1975	2292					29.1	2675	4165	5200
			Age (weeks pca)	34.6	35.6	36.6	37.3	38.6						40.6	48.6	55.6
Female	Control	9701-0005	Weight (g)	1174	1366	1555	1745	1976					28.3	3175	5140	6280
			Age (weeks pca)	30.7	31.7	32.7	33.7	34.7						39.7	48.4	56.4
Female	Control	9701-0008	Weight (g)	1391	1569	1898	2198	2406					41.1	2980	4425	5815
			Age (weeks pca)	34.3	35.3	36.4	37.3	37.9						40.4	47.4	56.4
Female	Control	9701-0011	Weight (g)	1050	1254	1492	1756	2044					36.6	2870	4420	5505
			Age (weeks pca)	30.6	31.4	32.4	33.4	34.4						39.7	48.6	57.4
Female	Control	9702-0002	Weight (g)	1222	1371	1570	1750	1995	2390				29.4	3380	4900	
			Age (weeks pca)	31.7	32.7	34.1	35.1	36.0	37.1					40.4	47.6	
Female	Control	9702-0004	Weight (g)	1454	1555	1840	2530						31.6	3600	5160	6900
			Age (weeks pca)	31.0	31.9	33.1	36.0							39.9	47.7	56.7
Female	Control	9702-0010	Weight (g)	1775	2065	2410	2645						42.2	3060	4820	6690
			Age (weeks pca)	34.0	35.0	36.0	37.0							39.9	48.3	57.6

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	Control	9703-0002	Weight (g) Age (weeks pca)	1170 29.1	1250 30.4	1390 31.3	1570 32.4	1825 33.4	2130 34.3				26.4	3210 39.6	4750 47.4	
Female	Control	9703-0005	Weight (g) Age (weeks pca)	1420 31.4	1590 32.3	1765 33.3	1900 33.9	2220 35.3					29.5	2610 37.3	4330 46.0	5640 55.0
Female	Control	9703-0008	Weight (g) Age (weeks pca)	1495 33.0	1715 34.0	2095 35.0	2445 36.0	2685 36.6					48.3	3360 40.1	4780 47.7	6410 56.1
Female	Control	9705-0004	Weight (g) Age (weeks pca)	1120 31.3	1290 32.3	1490 33.3	1660 34.0						28.3	2722 39.7	4085 46.6	5646 55.0
Female	Control	9706-0003	Weight (g) Age (weeks pca)	1515 35.1	1673 36.3	1965 37.1	2330 38.3					37.9				
Female	Control	9706-0005	Weight (g) Age (weeks pca)	1485 33.0	1610 33.7	1805 34.7	2150 36.0						31.7	2740 40.0	4165 48.1	5305 57.3
Female	Control	9706-0009	Weight (g) Age (weeks pca)	1525 32.3	1620 32.9	1960 34.3							31.6	3640 40.3	5495 47.6	7225 53.4
Female	Control	9706-0010	Weight (g) Age (weeks pca)	1905 34.3	2185 35.0								56.0	3655 40.0	5390 48.4	6535 56.7
Female	Control	9706-0013	Weight (g) Age (weeks pca)	1185 31.6	1270 32.4	1585 33.6	1810 34.6						31.1	2680 40.1	3800 48.4	
Female	Control	9706-0016	Weight (g) Age (weeks pca)	1510 32.0	1765 33.1	1935 33.9							32.6	3320 40.7	4535 48.7	5297 56.6
Female	Control	9707-0003	Weight (g) Age (weeks pca)	1465 32.0	1505 32.6	1655 33.6	2010 35.3	2325 36.4	2765 38.3				30.2	3110 40.1	4125 48.1	4995 57.1
Female	Control	9707-0006	Weight (g) Age (weeks pca)	1866 34.6	3430 40.0	3430 40.0							41.2	3430 40.0	5385 48.9	7250 57.3
Female	Control	9707-1006	Weight (g) Age (weeks pca)	1815 34.6	3330 40.0	3330 40.0							39.9	3330 40.0	5490 48.9	6920 57.3

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	Control	9708-0001	Weight (g) Age (weeks pca)	1410 33.4	1600 34.4	1850 35.4	2050 36.9						27.2	2910 40.6	4734 48.4	
Female	Control	9708-0003	Weight (g) Age (weeks pca)	940.0 30.0	970.0 31.0								4.3			
Female	Control	9708-0008	Weight (g) Age (weeks pca)	1380 32.9	1605 33.7	1860 34.9	2180 36.3						33.1	2582 39.3	4110 47.4	5361 57.1
Female	Control	9709-0002	Weight (g) Age (weeks pca)	1980 32.7	2225 33.7	2400 34.7							30.0			
Female	Control	9709-0005	Weight (g) Age (weeks pca)	1175 31.9	1425 33.3	1665 34.6	1945 35.6	2200 36.3					32.3	2975 39.6	4700 48.4	5900 56.7
Female	Control	9712-0005	Weight (g) Age (weeks pca)	972.0 29.1	1145 30.1	1290 31.1	1490 32.1	1695 33.1					25.6	2930 40.3	4450 47.6	5880 57.1
Female	Control	9712-0006	Weight (g) Age (weeks pca)	1203 31.9	1358 32.9	1585 33.9	1790 34.9						28.4	3030 39.7	4560 48.0	6230 57.0
Female	Control	9743-0003	Weight (g) Age (weeks pca)	1300 31.6	1520 33.4	1740 34.1	1890 35.1						24.0		4000 48.4	5160 57.4
Female	Control	9746-0001	Weight (g) Age (weeks pca)	1420 32.6	1740 33.6	2075 34.6	2320 35.6	2625 36.6					42.7	3170 39.7	4145 47.6	5192 56.6
Female	DIIA	9698-0004	Weight (g) Age (weeks pca)	1410 30.1	1650 31.1	1890 32.1	2140 33.1						34.7	3787 40.0	4795 48.0	6291 57.0
Female	DIIA	9698-0006	Weight (g) Age (weeks pca)	1110 30.7	1240 31.7	1420 32.7	1720 33.7						28.7			
Female	DIIA	9698-0009	Weight (g) Age (weeks pca)	1205 30.3	1310 31.4	1520 32.4	1630 33.1	2020 34.9					25.9	2891 40.0	3979 48.0	5121 57.0
Female	DIIA	9698-0307	Weight (g) Age (weeks pca)	1790 34.4	2110 35.7	2450 37.6							29.7	3135 39.4	5185 47.4	6695 56.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DIHA	9699-0002	Weight (g) Age (weeks pca)	1313 32.9	1477 33.9	1669 34.9	1929 35.9	2380 36.9					36.9	3177 39.7	5787 47.7	7093 56.7
Female	DIHA	9700-0001	Weight (g) Age (weeks pca)	1580 32.4	1820 33.4	2050 34.3	2295 35.3	2500 36.3					34.5	3210 40.1	5110 48.1	6300 57.1
Female	DIHA	9701-0001	Weight (g) Age (weeks pca)	1300 33.0	1356 34.0	1586 35.0	1924 36.0	2125 36.6					34.2	2910 39.6	4325 48.0	5625 57.0
Female	DHA	9701-0004	Weight (g) Age (weeks pca)	1108 30.7	1261 31.7	1441 32.7	1671 33.7	1897 34.7					28.4	3020 39.7	4855 48.4	6040 56.4
Female	DHA	9701-0012	Weight (g) Age (weeks pca)	1674 34.9	1928 35.9	2151 36.9	2311 37.6	2685 39.6	2685 39.6				30.1	2685 39.6		
Female	DIHA	9701-0014	Weight (g) Age (weeks pca)	1422 33.9	1631 34.9	1858 35.9	2455 37.9						37.2	2970 39.9	4605 47.7	5140 56.9
Female	DIHA	9702-0001	Weight (g) Age (weeks pca)	1780 31.6	2115 32.9	2390 33.9	3000 36.4						35.8	3850 40.0	5610 49.6	6600 57.0
Female	DIHA	9702-0006	Weight (g) Age (weeks pca)	1850 35.4	2005 36.1	2650 39.6	2650 39.6						27.3	2650 39.6	4450 48.4	6020 56.4
Female	DIHA	9702-0007	Weight (g) Age (weeks pca)	1285 31.1	1459 32.1	1780 33.6	1965 34.4	2035 34.9					29.6			
Female	DIHA	9702-0008	Weight (g) Age (weeks pca)	1605 34.1	1930 35.1	3540 39.6	3540 39.6						51.3	3540 39.6	5920 47.6	7820 57.1
Female	DIHA	9703-0003	Weight (g) Age (weeks pca)	1255 34.4	1355 35.1	1535 36.1	1845 37.1	2150 38.1					34.8	2430 39.4	4130 48.0	5010 56.1
Female	DIHA	9703-0004	Weight (g) Age (weeks pca)	1170 32.6	1340 33.3	1550 34.3	1795 35.3	2225 37.0					33.9	2870 39.4	4610 48.1	6490 57.1
Female	DHA	9703-0009	Weight (g) Age (weeks pca)	1570 33.3	1830 34.3	2095 35.1	2395 36.3	2655 37.9					34.6	3160 40.4	4480 48.4	5570 58.0

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA	9704-0004	Weight (g) Age (weeks pca)	1440 33.6	1670 34.6	1740 35.0							30.5	3100 40.0	5830 48.0	8630 57.0
Female	DHA	9704-0005	Weight (g) Age (weeks pca)	1050 29.7	1310 30.9	1490 31.7	1700 32.7	1890 33.7					30.0	3360 39.6	4860 48.0	6100 57.0
Female	DHA	9705-0001	Weight (g) Age (weeks pca)	1220 32.7	1370 33.6	1590 34.7	1880 35.7	2098 36.7					31.9	3092 40.1	4795 48.1	5986 57.1
Female	DHA	9706-0006	Weight (g) Age (weeks pca)	1270 33.0	1405 33.7	1630 34.7	1930 36.0						31.7	2705 40.0	4145 48.1	5320 57.3
Female	DHA	9706-0008	Weight (g) Age (weeks pca)	990.0 33.4	1188 34.6	1345 35.7	1485 36.4						23.0	2120 39.9		
Female	DHA	9706-0012	Weight (g) Age (weeks pca)	1610 31.6	1830 32.4	2130 33.6	2280 34.6						32.5	3530 40.1	4790 48.4	
Female	DHA	9706-0014	Weight (g) Age (weeks pca)	1080 31.3	1170 32.6	1395 33.4	1560 34.4	1804 35.3					26.2	3295 40.6	5600 49.4	7675 58.0
Female	DHA	9707-0004	Weight (g) Age (weeks pca)	1635 34.0	1771 35.0	2850 38.7							38.1	3045 40.0	4595 48.0	5765 57.0
Female	DHA	9707-0308	Weight (g) Age (weeks pca)	2005 34.4	3440 39.3	3440 39.3							42.2	3440 39.3	4800 47.3	6360 57.7
Female	DHA	9708-0004	Weight (g) Age (weeks pca)	1460 32.6	1665 33.6	1955 34.6	2280 35.6	2485 36.6					38.1			
Female	DHA	9708-0006	Weight (g) Age (weeks pca)	1485 33.7	1775 34.7	2110 35.7	2380 37.0						39.5	3010 40.1	4620 48.1	6530 57.0
Female	DHA	9709-0001	Weight (g) Age (weeks pca)	1250 29.6	1490 31.0	1755 32.0	1970 33.0	2250 34.0	2520 35.0				33.8	3500 40.1		
Female	DHA	9709-0003	Weight (g) Age (weeks pca)	1540 34.4	1725 35.4	2015 36.4	2155 37.4						30.5	2580 40.3	4080 47.7	5420 57.1

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA	9712-0001	Weight (g) Age (weeks pca)	987.0 30.0	1120 31.0	1270 32.0	1470 33.0	1685 34.0					24.9	2940 40.1	3980 48.1	5250 57.1
Female	DHA	9712-0002	Weight (g) Age (weeks pca)	1060 32.7	1230 33.7	1430 34.7							26.4			
Female	DHA	9712-0007	Weight (g) Age (weeks pca)	1082 32.7	1230 33.7	1440 34.7	1650 35.7						27.3	2425 39.7	4250 47.9	5340 56.9
Female	DHA	9743-0001	Weight (g) Age (weeks pca)	1000 32.1	1170 33.1	1470 34.4	1800 35.7	1930 36.1					33.5		4140 48.3	5400 57.3
Female	DHA	9743-0002	Weight (g) Age (weeks pca)	1380 32.1	1570 33.3	1845 34.1	1975 35.1						29.7		4540 48.4	5160 57.4
Female	DHA+ARA	9698-0001	Weight (g) Age (weeks pca)	1550 31.6	1690 32.6	2000 33.6	2380 34.9						37.1	3530 40.0	5348 47.7	6582 56.7
Female	DHA+ARA	9698-0002	Weight (g) Age (weeks pca)	1580 32.6	1870 33.7	2130 34.6	2260 35.7						31.8	3241 40.7		
Female	DHA+ARA	9699-0004	Weight (g) Age (weeks pca)	985.0 31.0	1122 32.0	1283 33.0	1536 34.0	1788 35.0					28.9	3177 41.3	5107 48.3	6979 57.3
Female	DHA+ARA	9699-0005	Weight (g) Age (weeks pca)	1330 31.9	1542 32.9	1688 33.9	2000 34.9	2330 35.9					35.1	4029 40.0	6752 48.0	8341 57.0
Female	DHA+ARA	9700-0002	Weight (g) Age (weeks pca)	1315 30.3	1525 31.3	1885 32.3	2035 33.3	2220 34.1	2480 35.6				31.9	3340 40.3	4930 48.1	6420 57.1
Female	DHA+ARA	9701-0002	Weight (g) Age (weeks pca)	1398 33.4	1609 34.4	1887 35.4	2210 36.4	2420 37.4					37.8	2930 39.4	5115 48.4	6525 56.4
Female	DHA+ARA	9701-0006	Weight (g) Age (weeks pca)	1720 32.3	1859 33.3	2113 34.3	2456 35.3	2728 36.1					38.3	3600 40.3	5045 48.0	6270 57.3
Female	DHA+ARA	9701-0007	Weight (g) Age (weeks pca)	1469 33.7	1427 34.9	1590 35.7	1982 36.7	2227 37.7					29.8	2680 39.9	4935 47.9	6955 56.9

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA+ARA	9701-0010	Weight (g) Age (weeks pca)	1488 32.3	1703 33.4	1978 34.4	2234 35.3	2433 36.1	2759 37.7				34.6	3500 41.1	5545 48.4	
Female	DHA+ARA	9701-0013	Weight (g) Age (weeks pca)	1841 33.0	2019 33.7								35.6		4545 48.7	5550 57.4
Female	DHA+ARA	9702-0003	Weight (g) Age (weeks pca)	1293 30.1	1488 31.1	1820 32.1	2155 33.4	2400 34.1					39.9	4190 40.0	6220 48.4	7500 56.9
Female	DHA+ARA	9702-0005	Weight (g) Age (weeks pca)	1895 34.0	2060 35.0	2300 36.0	2525 37.0	2710 38.0					29.9	3025 40.0	4300 47.4	5340 56.4
Female	DHA+ARA	9702-0009	Weight (g) Age (weeks pca)	1725 34.0	2000 35.0	2230 36.0	2595 37.0	2655 37.3					40.9	2905 39.9	4680 48.3	6410 57.6
Female	DHA+ARA	9703-0001	Weight (g) Age (weeks pca)	1145 31.3	1255 32.1	1450 33.1	1680 34.3	1955 35.3					28.9	3030 41.0	4250 48.1	5420 57.3
Female	DHA+ARA	9703-0006	Weight (g) Age (weeks pca)	1865 34.0	2200 35.0	2560 35.9	2880 37.0						49.1	3600 40.0	5400 48.1	6650 56.7
Female	DHA+ARA	9703-0007	Weight (g) Age (weeks pca)	1390 32.0	1495 33.1	1620 34.0	1880 35.0	2030 35.7	2240 36.6				27.4	2850 40.0	4190 47.9	5850 56.7
Female	DHA+ARA	9704-0002	Weight (g) Age (weeks pca)	960.0 29.0	1090 30.0	1200 30.9	1370 31.9	1570 32.9	1780 33.9	2070 34.9			26.7	3110 40.0	5150 48.0	6800 57.3
Female	DHA+ARA	9704-0003	Weight (g) Age (weeks pca)	1690 32.7	1840 33.4								30.0	4000 40.0	5400 48.0	6640 57.0
Female	DHA+ARA	9705-0003	Weight (g) Age (weeks pca)	1760 34.4	2260 35.7	2500 36.6	2920 37.7						49.8	3376 39.9	5107 48.4	6894 56.9
Female	DHA+ARA	9705-0005*	Weight (g) Age (weeks pca)	1075 31.1	1120 31.4	1185 31.7	1280 32.1	1310 32.4	1310 32.7	1265 33.0	1350 33.3	1380 33.4	22.1	2600 40.4	4000 48.0	5050 57.0
Female	DHA+ARA	9706-0001	Weight (g) Age (weeks pca)	1290 31.7	1515 32.9	1685 33.7	2060 34.9						34.5	4100 40.1	6550 48.6	7655 56.7

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA+ARA	9706-0002	Weight (g) Age (weeks pca)	1395 31.9	1710 33.0	1884 33.9	2275 35.4						34.8	2845 40.3	4645 48.9	5550 57.3
Female	DHA+ARA	9706-0004	Weight (g) Age (weeks pca)	1550 36.7	1705 37.6	2050 38.7							36.1	2645 41.7	4225 49.7	4935 58.0
Female	DHA+ARA	9706-0007	Weight (g) Age (weeks pca)	1235 33.4	1490 34.6	1820 35.7	1930 36.4						34.3	2505 40.3		
Female	DHA+ARA	9706-0011	Weight (g) Age (weeks pca)	1900 34.3	2105 35.0								41.0	3430 40.0	5175 48.4	6140 56.7
Female	DHA+ARA	9706-0015	Weight (g) Age (weeks pca)	1670 34.6	1975 35.6	2210 36.4							41.6	3005 40.9	4465 48.4	5810 57.6
Female	DHA+ARA	9706-0017	Weight (g) Age (weeks pca)	1465 32.3	1700 33.4	1895 34.3	2170 35.3						33.4			
Female	DHA+ARA	9707-0002	Weight (g) Age (weeks pca)	1775 34.3	2240 36.0	2385 36.9	2610 37.9						33.2			
Female	DHA+ARA	9708-0002	Weight (g) Age (weeks pca)	1535 33.0	1700 34.0	1980 35.0	2200 36.0						32.5	2724 38.1	4645 47.6	6315 55.4
Female	DHA+ARA	9708-0005	Weight (g) Age (weeks pca)	1125 32.4	1345 33.4	1610 34.4	1980 35.4						40.4	3121 39.4	5855 47.4	7875 57.4
Female	DHA+ARA	9708-0007	Weight (g) Age (weeks pca)	1200 31.3	1440 32.3	1680 33.3	1975 34.3						36.6			
Female	DHA+ARA	9709-0004	Weight (g) Age (weeks pca)	1350 31.9	1560 33.3	1885 34.6	2250 35.6	2475 36.3					37.0	3295 39.7	5250 48.4	6685 56.7
Female	DHA+ARA	9712-0003	Weight (g) Age (weeks pca)	1283 32.0	1410 33.0	1590 34.0	1850 35.0	2010 36.0					27.1	2580 40.0	4130 48.2	5640 57.5
Female	DHA+ARA	9712-0004	Weight (g) Age (weeks pca)	1575 33.0	1780 34.0	1890 34.6	2080 35.6	2530 37.6					29.7	3220 40.3	4920 48.1	6600 57.1

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA+ARA	9712-0008	Weight (g) Age (weeks pca)	1590 34.0	1780 35.0	1990 35.8	2475 37.4						37.2	2960 40.1	4470 48.1	5760 57.1
Female	DHA+ARA	9746-0002	Weight (g) Age (weeks pca)	1249 32.7	1429 33.7	1597 34.7	1814 35.7	2110 36.7					30.1	2680 39.9	4010 46.9	5362 56.9
Female	IIM	9698-0501												3546 40.0	4880 48.3	
Female	IIM	9698-0502												3518 40.0	5972 47.9	
Female	IIM	9698-0503												3390 40.0	4213 48.3	5319 57.1
Female	IIM	9698-0504												3383 40.0	5234 48.7	6667 57.9
Female	IIM	9698-0505												3646 40.0	4638 48.3	5653 57.0
Female	IIM	9699-0601												2582 40.0	4766 49.0	5731 57.0
Female	IIM	9699-0602												4284 40.0	4823 48.0	5986 57.0
Female	IIM	9699-0603												3716 40.0	4482 47.7	5674 56.7
Female	IIM	9699-0604												3660 40.0	4738 48.0	6355 57.0
Female	IIM	9699-0605												3433 40.0	5617 48.4	7603 57.6
Female	IIM	9701-0501												3884 40.0	5630 47.7	6450 57.7

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	HM	9701-0502												3858 40.0	5420 48.6	6700 57.6
Female	HM	9701-0503												3430 40.0	4265 47.4	5085 57.4
Female	HM	9701-0504												3317 40.0	5020 48.1	6230 57.1
Female	HM	9702-0501												3302 40.0	5540 47.7	6630 56.7
Female	HM	9702-0502												2658 40.0	5310 47.4	6800 57.1
Female	HM	9702-0503												2895 40.0	3430 47.7	4530 57.4
Female	HM	9702-0504												3401 40.0	5390 48.0	6270 57.4
Female	HM	9702-0505												3141 40.0	4210 47.9	5320 57.0
Female	HM	9702-0506												3762 40.0	6040 48.9	7600 57.7
Female	HM	9702-0507												2718 40.0	4050 48.9	4940 57.4
Female	HM	9702-0508												2927 40.0	4240 47.4	5860 57.0
Female	HM	9703-0501												4085 40.0	5260 48.1	6360 57.1
Female	HM	9703-0505												3390 40.0	5760 48.3	7670 57.3

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	IIM	9703-0506												3405 40.0	6170 47.9	7490 56.9
Female	IIM	9703-0507												3085 40.0	5090 48.0	6550 56.3
Female	IIM	9704-0501												3194 40.0	4700 48.1	5880 57.4
Female	IIM	9705-0501												3120 40.0	4500 48.1	5702 57.1
Female	IIM	9705-0502												4080 40.0	6327 48.3	7348 57.3
Female	IIM	9706-0501												3396 40.0	5000 48.3	6645 58.1
Female	IIM	9706-0502												3041 40.0	4315 47.7	5525 57.6
Female	IIM	9707-0501												4653 40.0	5515 47.9	6770 56.6
Female	IIM	9707-0502												3419 40.0	5500 48.0	7080 57.1
Female	IIM	9707-0503												3773 40.0	5785 47.9	7675 56.9
Female	IIM	9707-0505												3716 40.0		
Female	IIM	9708-0501												3688 40.0	5440 48.1	6890 57.6
Female	IIM	9708-0502												3454 40.0	5192 48.1	5950 57.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	HM	9708-0503												2977 40.0	5165 48.1	7040 57.4
Female	HM	9708-0504												3864 40.0	5660 48.4	6705 57.4
Female	HM	9708-0505												3831 40.0	5800 47.7	7435 57.6
Female	HM	9709-0501												3550 40.0		
Female	HM	9709-0502												3715 40.0	5205 48.0	6100 56.9
Female	HM	9709-0503												3195 40.0		
Female	HM	9709-0504												3190 40.0	4590 48.3	
Female	HM	9709-0506												3505 40.0	4500 48.0	5910 57.1

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\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	SUBJECT	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Wgt10	Wgt11	Wgt12	Wgt13	Wgt14	Wgt15	Wgt16	Wgt17	Wgt18	Growth Rate g/day
Male	Control	9712-0301	Weight (g) Age (weeks pca)	1245 31.6	1221 31.7	1245 31.9	1291 32.0	1294 32.1	1330 32.3	1369 32.4	1402 32.6	1433 32.7	1448 32.9	1465 33.0								26.1
Male	DIHA	9707-0307	Weight (g) Age (weeks pca)	1649 32.4	1675 32.6	1699 32.7	1732 32.9	1778 33.0	1811 33.1	1858 33.3	1882 33.4	1938 33.6	1994 33.7	2030 33.9	2075 34.0							39.6
Female	Control	9698-0003	Weight (g) Age (weeks pca)	1020 31.1	1050 31.3	1070 31.4	1080 31.6	1080 31.7	1060 31.9	1080 32.0	1070 32.1											5.6
Female	DIHA+ARA	9705-0005	Weight (g) Age (weeks pca)	1075 31.1	1120 31.4	1185 31.7	1280 32.1	1310 32.4	1310 32.7	1265 33.0	1350 33.3	1380 33.4	1440 33.7	1450 33.9	1510 34.0	1515 34.1	1565 34.3	1585 34.4	1640 34.6	1680 34.7	1670 34.9	22.1

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What is claimed is:

1. A method for enhancing the growth of preterm infants comprising administering to said infants a growth enhancing amount of DHA and ARA.
2. The method of Claim 1 wherein DHA and ARA are supplemented into infant formula.
3. The method of Claim 1 wherein the ratio of ARA:DHA is 1:2 to 5:1.
4. The method of Claim 1 wherein the ratio of ARA:DHA is 1:1 to 3:1.
5. The method of Claim 1 wherein the ratio of ARA:DHA is about 2:1.
6. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 2 mg/100 kcal to about 50 mg/100 kcal and ARA in an amount of about 4 mg/100 kcal to about 100 mg/100 kcal.
7. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 5 mg/100 kcal to about 33 mg/100 kcal and ARA in an amount of about 10 mg/100 kcal to about 67 mg/100 kcal.

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8. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 15 mg/100 kcal to about 20 mg/100 kcal and ARA in an amount of about 30 mg/100 kcal to about 40 mg/100 kcal.
9. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 9 months corrected age.
10. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 6 months corrected age.
11. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 4 months corrected age.
12. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 2 months corrected age.
13. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is no greater than term corrected age.

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# Premature Infant Weight Gain

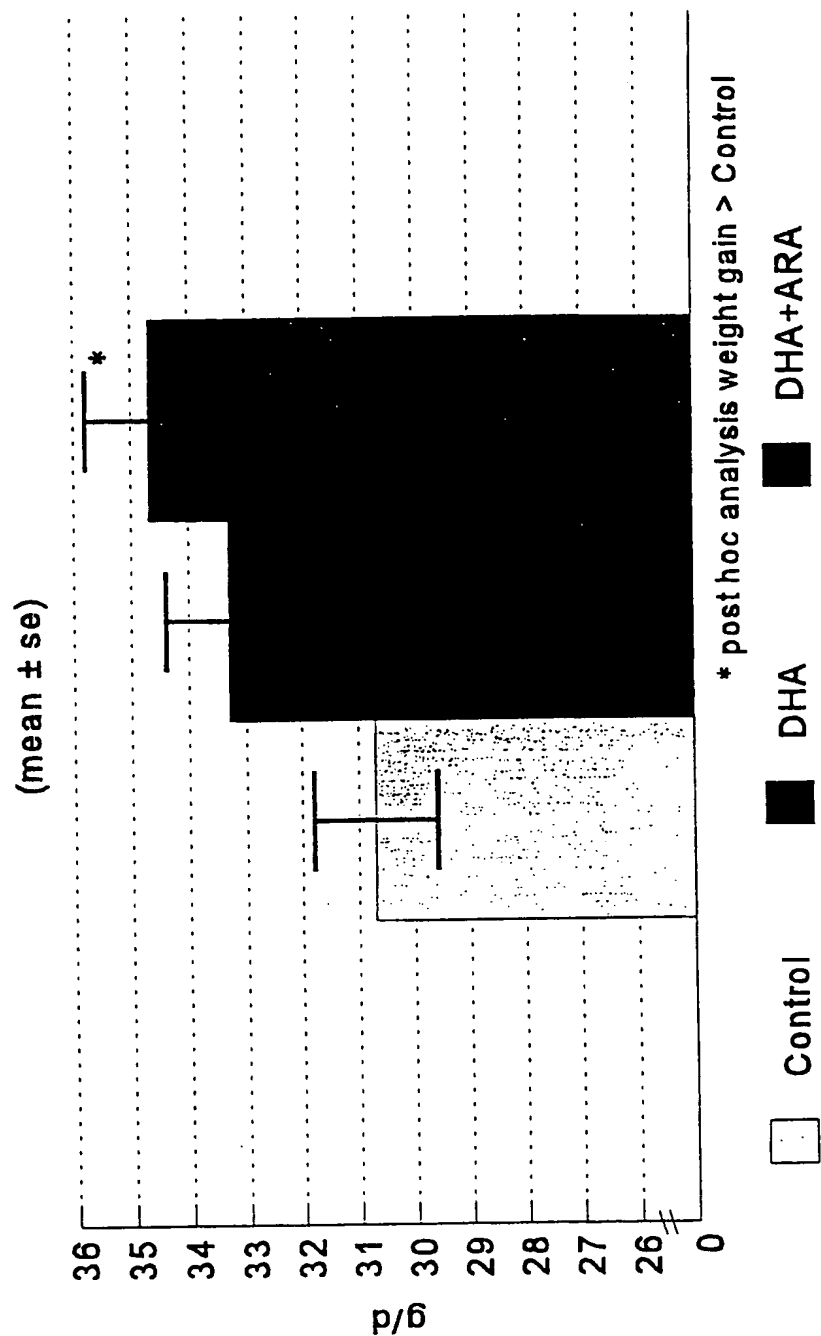


Figure 1.

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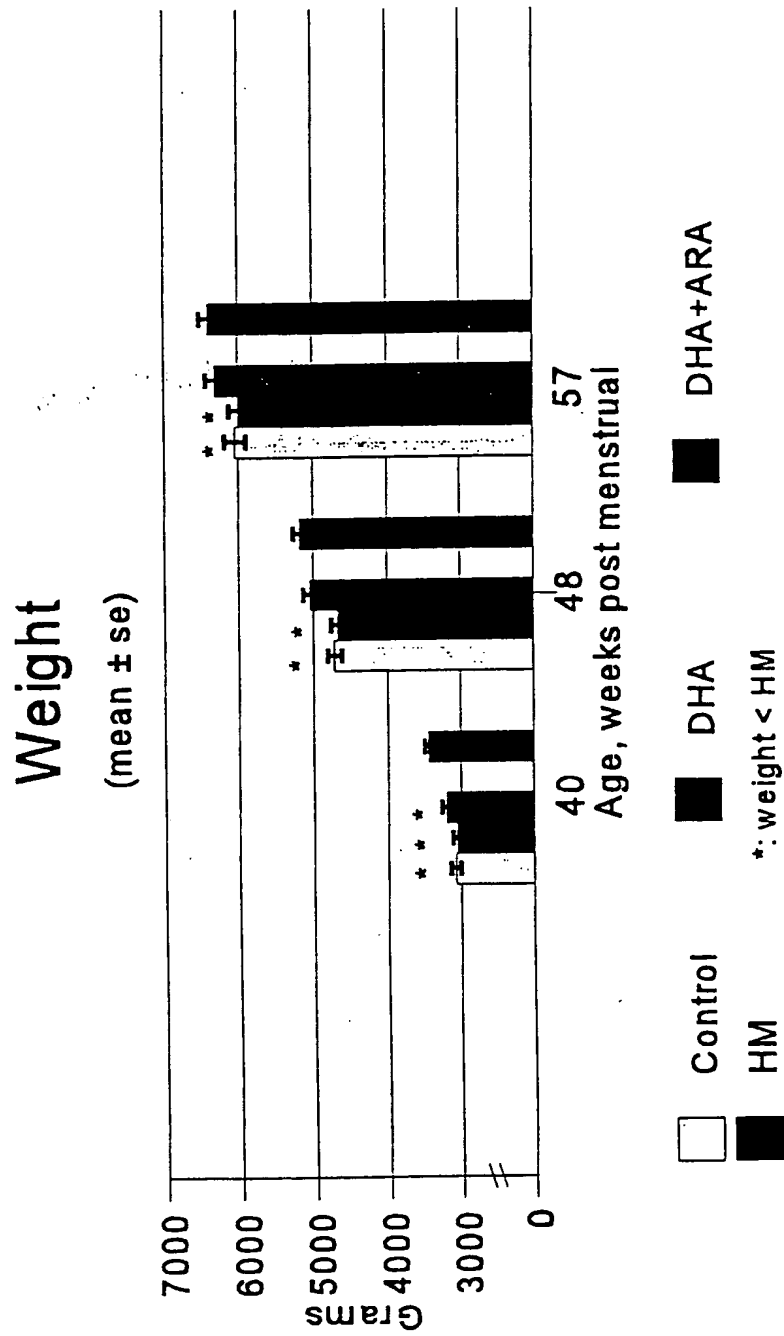
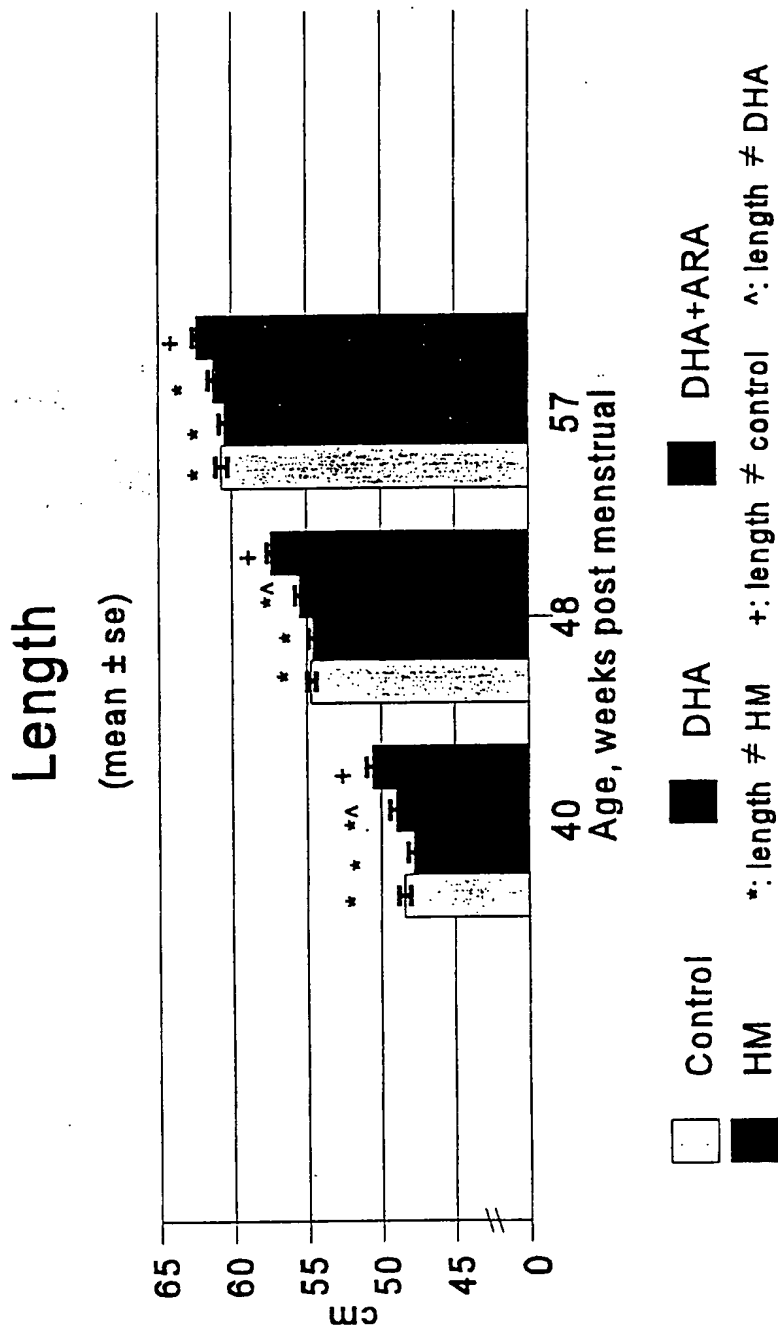


Figure 2.

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Figure 3.



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# Head Circumference

(mean  $\pm$  se)

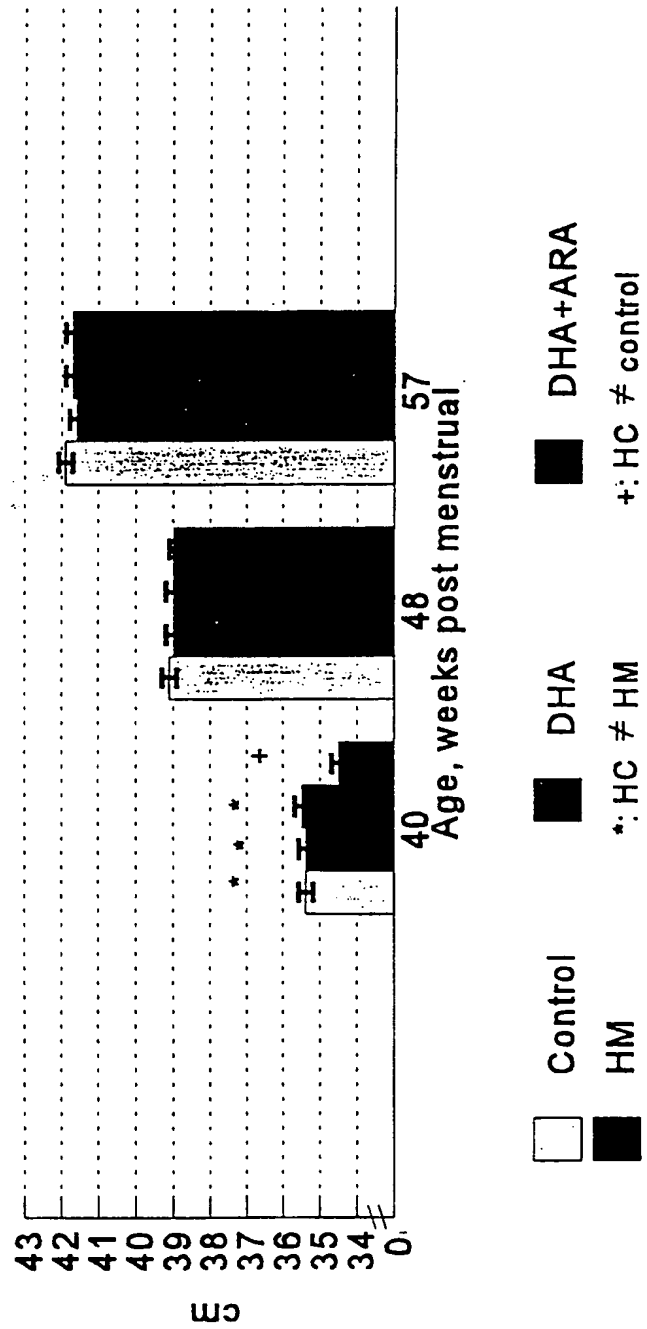
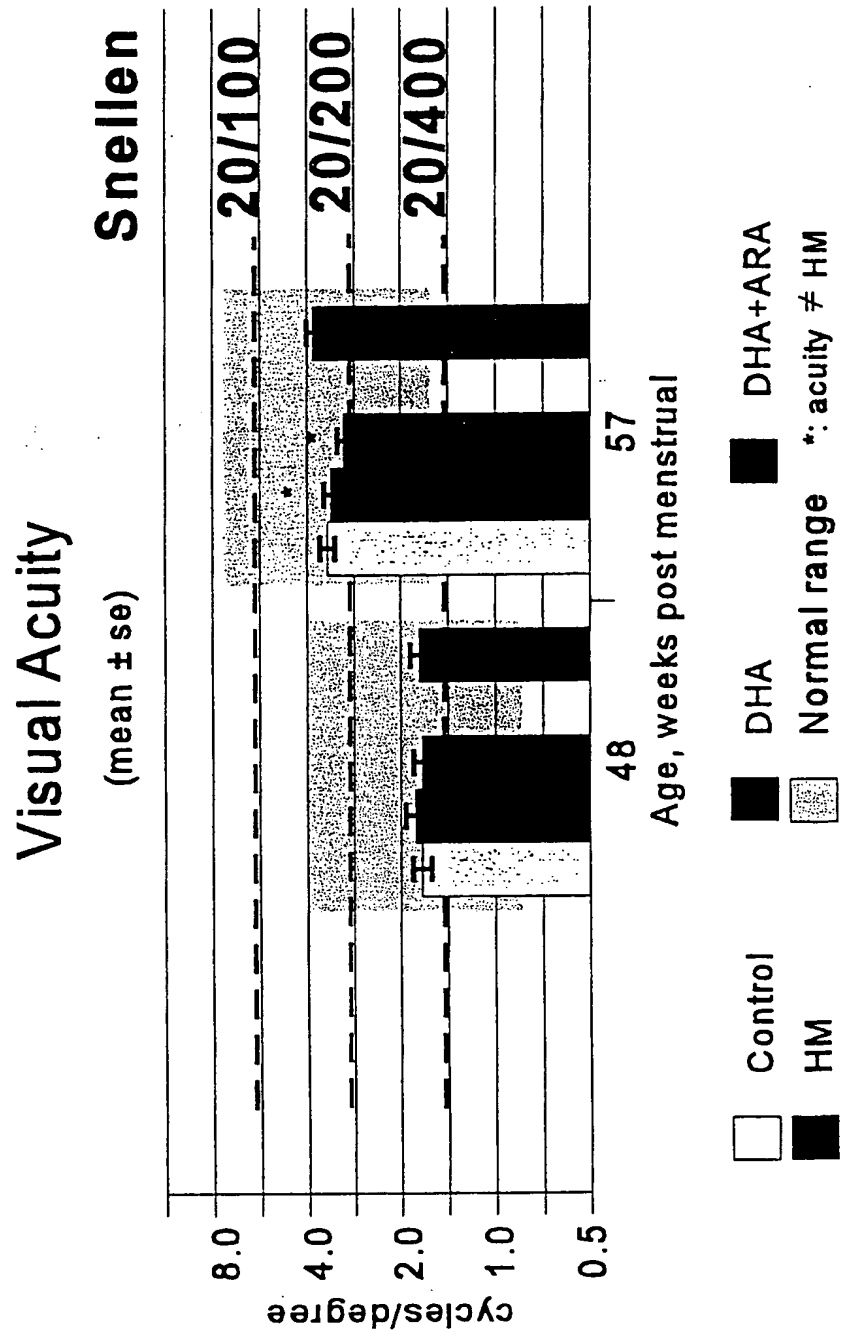


Figure 4.

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Figure 5.



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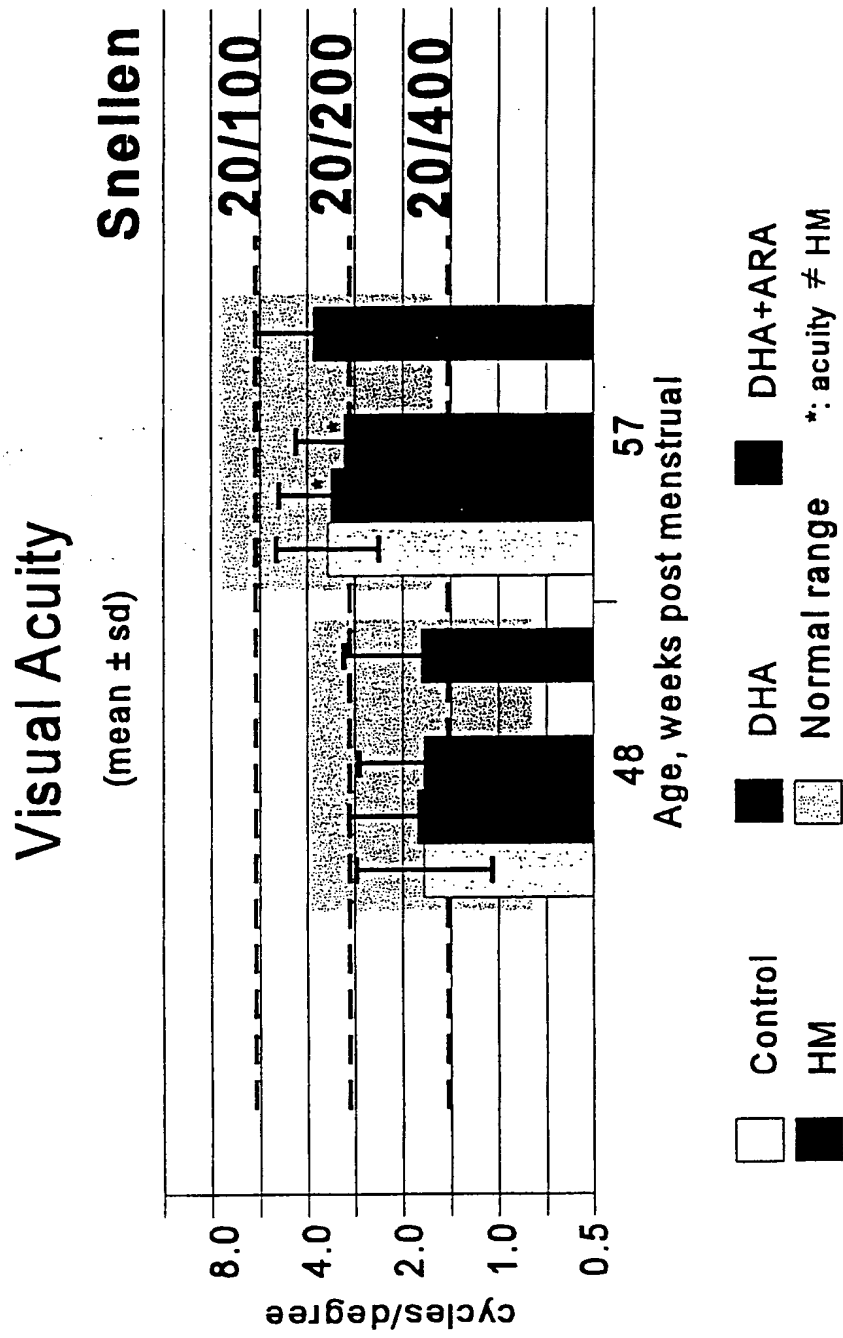


Figure 6.

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/20</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/44917</b>  (43) International Publication Date: 15 October 1998 (15.10.98)
<p>(21) International Application Number: PCT/US98/10566</p> <p>(22) International Filing Date: 20 March 1998 (20.03.98)</p> <p>(30) Priority Data: 60/042,366 27 March 1997 (27.03.97) US</p> <p>(71) Applicant (for all designated States except US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 06543 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SCHADE, Deborah, A. [US/US]; 8100 Upper Mt. Vernon Road, Evansville, IN 47712 (US). MERKEL, Kimberly, L. [US/US]; 6616 Whetstone Road, Evansville, IN 47711 (US). HANSEN, James, W. [US/US]; 5600 Spring Park Drive, Evansville, IN 47711 (US).</p> <p>(74) Agents: ROESLER, Judith, A. et al.; Mead Johnson Nutritional, 2400 West Lloyd Expressway, Mailcode A-21, Evansville, IN 47721 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
(54) Title: USE OF DOCOSAHEXANOIC ACID AND ARACHIDONIC ACID ENHANCING THE GROWTH OF PRETERM INFANTS		
<p>(57) Abstract</p> <p>A method for enhancing the growth of preterm infants involving the administration of certain long chain polyunsaturated fatty acids. It is preferred that the infants are administered an infant formula containing a combination of docohexaenoic acid and arachidonic acid.</p>		

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## USE OF DOCOSAHEXANOIC ACID AND ARACHIDONIC ACID ENHANCING THE GROWTH OF PRETERM INFANTS

Field of Invention

The present invention concerns enhancing the growth of preterm infants involving administration of infant formula containing a combination of docosahexaenoic and arachidonic acid.

Background of the Invention

The long chain polyunsaturated fatty acids (LC PUFA) have been shown to be important in infant development. Particularly, arachidonic acid (ARA) and docosahexaenoic acid (DHA) are LC PUFA that are of special interest in infant nutrition because they are found in high concentrations in the brain (Sastry PS, Lipids of nervous tissue: composition and metabolism. Progress Lipid Res 1985;24:69-176) and the retina (Fliesler SJ and Anderson RE. Chemistry and metabolism of lipids in the vertebrate retina. Progress Lipid Res 1983;22:79-131). ARA (20:4n-6) and DHA (22:6n-3) are derived from the parent essential fatty acids linoleic acid (18:2n-6) and  $\alpha$ -linolenic acid (18:3n-3) through alternate desaturation and elongation and accumulate rapidly in fetal neural tissue during the last months of gestation and the first months of postnatal life (Makrides M, Neuman MA, Byard RW, Simmer K, Gibson RA. Fatty composition of the brain, retina and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189-94).

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Unlike term infants, preterm infants do not fully benefit from the maternal and placental LC PUFA supply during the last trimester of pregnancy. Even though preterm infants are capable of synthesizing both DHA and ARA from their 18 carbon precursors (Carnielli VP, Wattimena DJL, Luijendijk IHT, Boerlage A, Degenhart HJ, Sauer PJJ. The very low birth weight premature infant is capable of synthesizing arachidonic and docosahexaenoic acids from linoleic and linolenic acids. *Pediat Res* 1996;40:169-174), it remains unclear whether the rate of synthesis is adequate to meet the optimal needs for central nervous system accretion in the absence of a dietary supply of these fatty acids. Preterm infants are dependent on their own dietary supply of linoleic and  $\alpha$ -linolenic acids through either human milk, which also contains small but significant amounts of ARA and DHA or through commercially available artificial formulas, none of which in the United States contain ARA and DHA.

It has been demonstrated in recent studies (Hoffman DR and Uauy R. Essentiality of dietary  $\omega$ -3 fatty acids for premature infants: Plasma and red blood cell fatty acid composition. *Lipids* 1992;27:886-95) that the fatty acid composition of red blood cell membrane lipids in infants receiving formulas supplemented with DHA (0.35% of total fatty acids) was similar to human milk-fed infants. In the same study, Birch (Birch DG, Birch EE, Hoffman DR, Uauy RD. Retinal development in very-low-birth-weight infants fed diets differing in Omega-3 fatty acids. *Investigation Ophthalmology Visual Science* 1992;33:2365-76) found that retinal function improved with the provision of a dietary supply of DHA in very low birth weight infants.



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The first year growth of preterm infants fed standard formula compared to marine oil LC PUFA supplemented formula was studied by Carlson et al. (Carlson SE, Cooke, RJ, Werkman SH, Tolley EA. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. *Lipids* 1992;27:901-907). The experimental formulas provided 0.2% of total fatty acids as DHA and also provided 0.3% as EPA (20:5n-3). This EPA concentration is higher than found in human milk while the DHA level is similar to human milk. Beginning at 40 weeks from conception, marine oil supplemented infants compared to controls had significantly lower weight, length, and head circumference. From this study, Carlson (Carlson SE, Werkman SH, Peeles JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci USA* 1993;90:1073-77) hypothesized that dietary ARA could improve first year growth of preterm infants, in the context of restoring growth to the level of control formula containing no LC PUFA.

In another study (Montalto, FB, et al., *Pediatric Research*, Vol 39, page 316A, abstract no. 1878) it was shown that male infants fed marine oil supplemented formula (containing DHA but essentially no ARA) had, by 4 to 6 months, lower head circumference, length, weight and fat free mass than standard formula fed infants. A third study also showed decreased weight at 9 and 12 months corrected age in preterm infants fed marine oil supplemented formula (with LC PUFA) to 2 months corrected age compared with control formula containing no LC PUFA (Carlson SE, et al., *Am. J. Clin. Nutr.*, 63 pp 687-97, 1996).

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The prior art has demonstrated that infants with altered tissue LC PUFA levels, resulting from a lack of LC PUFA in their diets, may be at risk for neurological problems, may also have reduced scores on cognitive tests, and may have lower retinal development than human milk-fed infants. Worldwide regulatory organizations such as the WHO/FAO Expert Committee on Fats and Oils in Human Nutrition have recommended that LC PUFA be included in preterm infant formula. These recommendations have been made despite the negative effects observed of DHA supplements on growth. There has been no demonstration in the literature that ARA and DHA, particularly when added to infant formula, enhances the growth of infants above that demonstrated by control formulas not containing ARA and DHA.

#### Summary of the Invention

It has unexpectedly been discovered that preterm infants receiving infant formula supplemented with both DHA and ARA demonstrate enhanced growth. The present invention is directed to enhancing the growth of preterm infants comprising administering to said infants a growth enhancing amount of DHA and ARA.

#### Detailed Description of the Invention

As reported in a review of preterm infant growth by Carlson, SE, (The Jnl of Pediatrics, vol 125, pp 533-8, 1994) "After adjusting for postconceptional age, preterm infants show a decline (rather

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than a catch-up) in the normalized weight from approximately 2 to 4 months past expected term.”

Several prior art studies have documented the value of administering DHA to infants. However, when DHA, either as the primary LC PUFA or combined with EPA, is administered to preterm infants, said infants suffer from decreased growth. It has been suggested that ARA may be beneficial to growth; however, heretofore the growth effects of administering both DHA and ARA to preterm infants have been unknown. It has been surprisingly discovered that administering the combination of ARA and DHA results in enhanced growth of infants relative to infants fed DHA alone. It has also been discovered that preterm infants administered an infant formula containing ARA and DHA exhibit enhanced growth relative to preterm infants fed control formula without DHA and ARA, such as those formulas currently used in modern nurseries. It has further been discovered that practice of the method of the invention results in growth of preterm infants catching up in an unexpected short time to a reference group of normal term breast fed infants.

The time to achieve growth similar or equivalent to normal term breast fed infants by practice of the method of the invention is less than 9 months corrected age; preferably less than 6 months corrected age, more preferably less than 4 months corrected age, even more preferably less than 2 months corrected age, and most preferably no greater than term corrected age.

The method of the invention requires a combination of DHA and ARA. The weight ratio weight of ARA:DHA can be about 1:2 to about 5:1, preferably about 1:1 to about 3:1, and more preferably

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about 2:1.

In the method of the invention the combination of DHA and ARA is preferably administered as part of an infant formula. The infant formula for use in the present invention is preferably nutritionally complete and typically contains suitable types and amounts of lipid, carbohydrate, protein, vitamins and minerals. The amount of lipid or fat typically can vary from about 3 to about 7 g/100 kcal. The amount of protein typically can vary from about 1 to about 5 g/100 kcal. The amount of carbohydrate typically can vary from about 8 to about 12 g/100 kcal. Protein sources can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, amino acids, and the like. Carbohydrate sources can be any used in the art, e.g., lactose, glucose, corn syrup solids, maltodextrins, sucrose, starch, rice syrup solids, and the like. Lipid sources can be any used in the art, e.g., vegetable oils such as palm oil, soybean oil, palmolein, coconut oil, medium chain triglyceride oil, high oleic sunflower oil, high oleic safflower oil, and the like. Conveniently, commercially available infant formula can be used. For example, Enfamil®, Enfamil® Premature Formula, Enfamil® with Iron, Lactofree®, Nutramigen®, Pregestimil®, ProSobee® (available from Mead Johnson & Company, Evansville, Indiana, U.S.A.), Similac®, Isomil®, Alimentum®, Neocare®, and Similac® Special Care (available from Ross Laboratories, Columbus, Ohio, U.S.A.), may be supplemented with suitable levels of ARA and DHA at the proper ratios and used in practice of the method of the invention.

The form of administration of the DHA and ARA in the method of the invention is not critical, as

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long as a growth enhancing amount is administered. Most conveniently, the DHA and ARA are supplemented into infant formula which is then fed to the infants. Alternatively, the DHA and ARA can be administered as a supplement not integral to the formula feeding, for example, as oil drops, sachets, in combination with other nutrient supplements such as vitamins, and the like.

The growth enhancing amount of DHA is typically about 2.5 mg/kg of body weight/day to about 60 mg/kg of body weight/day, preferably about 6 mg/kg of body weight/day to about 40 mg/kg of body weight/day, more preferably about 12 mg/kg body weight/day to about 30 mg/kg body weight/day, and even more preferably about 18 mg/kg of body weight/day to about 24 mg/kg of body weight/day.

The growth enhancing amount of ARA is typically about 5 mg/kg of body weight/day to about 120 mg/kg of body weight/day, preferably about 12 mg/kg of body weight/day to about 80 mg/kg of body weight/day, more preferably about 24 mg/kg body weight/day to about 60 mg/kg body weight/day, and even more preferably about 36 mg/kg of body weight/day to about 48 mg/kg body weight/day.

The amount of DHA in infant formulas for use in the present invention typically varies from about 2 mg/100 kilocalories (kcal) to about 50 mg/100 kcal, preferably about 5 mg/100 kcal to about 33 mg/100 kcal, more preferably about 10 mg/100 kcal to about 25 mg/100 kcal, and even more preferably about 15 mg/100 kcal to about 20 mg/100 kcal.

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The amount of ARA in infant formula for use in the present invention typically varies from about 4 mg/100 kcal to about 100 mg/100 kcal, preferably about 10 mg/100 kcal to about 67 mg/100 kcal, more preferably about 20 mg/100 kcal to about 50 mg/100 kcal, and even more preferably about 30 mg/100 kcal to about 40 mg/100 kcal.

The infant formula supplemented with oils containing DHA and ARA for use in the present invention can be made using standard techniques known in the art. For example, replacing an equivalent amount of an oil normally present, e.g., high oleic sunflower oil.

The source of the ARA and DHA can be any source known in the art such as fish oil, single cell oil, egg yolk lipid, brain lipid, and the like. The DHA and ARA can be in natural form, provided that the remainder of the LC PUFA source does not result in any substantial deleterious effect on the infant. Alternatively, the DHA and ARA can be used in refined form. It is preferred that the LC PUFA used in the invention contain little or no EPA. For example, it is preferred that the infant formulas used herein contain less than about 20 mg/100 kcal EPA; preferably less than about 10 mg/kcal EPA; more preferably less than about 5 mg/100 kcal EPA; and most preferably substantially no EPA.

Preferred sources of DHA and ARA are single cell oils as taught in U.S. patent nos. 5,374,657, 5,550,156, and 5,397,591, the disclosures of which are incorporated herein by reference in their entirety.

The following examples are to illustrate the invention but should not be interpreted as a limitation thereon.

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EXAMPLES

## I

CLINICAL STUDY DESIGN

## 1. INTRODUCTION

This study is a double-blind, randomized, controlled parallel design, prospective trial of premature infant formulas containing microalgae and fungi-derived oils which contain a part of their constituents arachidonic acid and docosahexaenoic acid. Formula feeding subjects will be randomized into one of 3 feeding groups:

- . premature formula plus DHA (about 0.13% of energy) and ARA (about 0.26% of energy)
- . premature formula plus DHA (about 0.13% of energy)
- . premature formula WITHOUT DHA and ARA

The products have the same nutrient composition (see Appendix A) and differ only in the level of DHA and ARA. The products will be blinded. The present order of formula has no relationship to randomization.

Normal, term, breast fed infants will be enrolled to provide a normal visual acuity reference.

Fifty evaluable subjects will be completed in each group. Premature infants will remain on study formulas after reaching 90 kcal/kg/d for a minimum of 28 days or until hospital discharge whichever is longer. After 28 days or discharge, whichever is longer, all premature infants will receive Enfamil or Enfalac with Iron. If medically indicated, ProSobee, Lactofree, Alactamil, Nutramigen, or Pregestimil may be used in place of Enfamil or Enfalac with Iron. Term infants will receive at least 85% of their nutrition from breast milk. Primary measures of effectiveness will include visual acuity and red blood cell membrane fatty acid profiles (i.e. DHA and ARA levels). The measure of safety will be growth and adverse experience reports.

## 2. SUBJECTS

## 2.1 SOURCE AND CHARACTERIZATION OF STUDY GROUP

Acceptable preterm subjects will be relatively healthy premature infants taking

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preterm formula. Anticipated hospitalization should be sufficient to allow for 28 days of enteral intake  $\geq 90$  kcal/kg/d and  $\geq 85\%$  study formula intake. All races and both sexes will be eligible for the study.

## 2.2 INCLUSION CRITERIA

### Preterm infants

- . Birth weight  $\geq 900$  g
- . Formula feeding at time of study enrollment
- . Anticipate enteral intake of  $\geq 90$  kcal/kg/day for  $\geq 28$  days before discharge home
- . Informed consent obtained

### Term Infants:

- . 38 to 42 weeks gestation
- . Committed to breast feeding
- . Informed Consent obtained

## 2.3 EXCLUSION CRITERIA

### Preterm infants

- .  $\geq 1500$  g at birth

### Preterm and Term Infants:

- . History of underlying disease or congenital malformation which in the opinion of the investigator is likely to interfere with the evaluation of the subject
- . More than 24 days between birth and full oral feeds ( $\geq 90$  kcal/kg/d)
- . Small ( $<10$ th percentile) for gestational age at birth (SGA)
- . Necrotizing enterocolitis as diagnosed by the physician



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Other gastrointestinal disease

Impaired visual or ocular status at birth

## 2.4 CONCOMITANT MEDICATIONS, HOSPITALIZATIONS, ILLNESSES

No medication which may effect FPL response may be used within 3 days of measurement.

No evidence of viral or bacterial infection during FPL testing.

No medications known to effect lipid metabolism (e.g., heparin at therapeutic levels)

## 3. STUDY PRODUCT INFORMATION

### 3.1 FORMULATIONS

Nutrient composition is included as Appendix A.

## 4. STUDY PROCEDURES

### 4.2.1 ENROLLMENT

Enrollment will take place over a 6 month period. Ideally, sufficient subjects will be enrolled so that 10 subjects in each group complete the study at each site for the multi-center trial. A total of 50 infants per formula group will complete this trial.

### 4.2.2 SCHEDULE OF EVENTS (SEE FLOW CHART, SECTION 8.4)

#### 4.2.2.1 RECRUITMENT

Mothers of eligible, healthy, preterm formula fed infants and term, breastfed infants will be contacted, the study explained to them, and if they are agreeable, written informed consent obtained.

Term infants may be enrolled anytime from birth until or during the 48 week visit.

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#### 4.2.2.2 RANDOMIZATION

Recruited formula fed subjects will be randomized into study groups. Randomization can occur anytime after enteral feeds reach 50 kcal/kg/day until commencement of full enteral feeds (i.e.,  $\geq 90$  kcal/kg/day).

#### 4.2.2.3 FEEDING

All premature infants will receive their assigned study formula after informed consent has been granted and enteral feeds are at least 50 kcal/kg/day. The infant will remain on study formula 28 days after reaching 90 kcal/kg/d or until hospital discharge, whichever is longer. Oral feeding amount, strength and rate will advance as appropriate for the clinical management of the infant.

All parents will be instructed not to feed solid foods during the study. The parents will be instructed that the study formula or breast milk is to serve as the sole source of food from enrollment to study end.

#### 4.2.2.4 BASELINE DATA COLLECTION

The following data will be collected by the Investigator at the time of enrollment and randomization on the case report forms:

- . Informed consent of parent obtained.
- . Post conceptual age.
- . That the subject is a premature infant, with Birth weight  $\geq 900$  gm and  $\geq 1500$  gm or a normal term infant between 38 and 42 weeks gestational age.
- . That the preterm subject is receiving infant formula or term infant is committed to breast feeding.
- . Anticipated preterm infant enteral intake of  $\geq 90$  kcal/kg/day for  $\geq 28$  days prior to discharge home.
- . That the subject has no history of underlying disease, inborn error of metabolism, or congenital malformation which in the opinion of the Investigator is likely to interfere with the evaluation of the study formulas.

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- . That the subject is not small (<10th percentile) for gestational age at birth.
- . That the subject does not have necrotizing enterocolitis as diagnosed by a physician.
- . That the subject does not have a gastrointestinal disease.
- . No more than 24 days between birth and full enteral feeds (i.e.,  $\geq 90$  kcal/kg/day).
- . That the subject did not have impaired visual or ocular status at birth.
- . Birth date, sex, race.
- . Birth weight, length and head circumference

#### 4.2.2.5 INVESTIGATOR PERIODIC DATA COLLECTION

"During hospitalization, preterm subjects will have their weight recorded daily while they are receiving study formula. Length and head circumference will be recorded weekly, along with an additional weight measurement. For a given subject, the same scale should be used for the weekly weight measurement."

"Weight, length, and head circumference will also be recorded at the 40, 48, and 57 week post conceptual age visit (preterm) and 56 and 119 days of age visit (term)."

#### 4.2.2.6 BLOOD DRAW

When preterm infant enrolls in the study and again at termination of study formula (i.e., hospital discharge or 28 days after reaching 90 kcal/kg/d of study product), the Investigator will ascertain that the infant is essentially solely formula fed. If this criteria is met, 1.2 ml/blood will be drawn for blood lipids. The sample will be processed as described in Appendix B.

An attempt will also be made to draw a similar blood sample at the 48 weeks PCA visit when visual acuity is measured in both term and preterm infants.

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#### 4.2.2.7 VISUAL ACUITY BY FORCED CHOICE PREFERENTIAL LOOKING (FPL) AT 48 AND 57 WEEKS $\pm$ 4 DAYS POST-CONCEPTUAL AGE

When the infant is 48 and 57 weeks  $\pm$  4 days post-conceptual age, trained persons at each study site will follow the Teller Acuity Card Procedure for the measurement of visual acuity of all study subjects. It is essential that only persons who are trained in the FPL procedure for determining visual acuity do the testing. If necessary, training of responsible persons and documentation of completion of successful training will be done at Children's Hospital Medical Center Ophthalmology Department in Seattle, Washington, according to the procedure attached as Appendix C.

If the infant cannot complete the procedure at 48 or 57 weeks  $\pm$  4 days postconceptual age (i.e., too fussy, too sleepy, too inattentive) the test should be repeated within 7 days.

#### 4.2.2.8 INTERIM EVALUATION

At preterm infant hospital discharge or 28 days after reaching 90 kcal/kg/d of study formula feeding, whichever is longer, the investigator will fill out an "Interim Evaluation" form. After reviewing the subject's records and discussion with the parents and staff, the investigator will indicate whether:

- . Whether or not the subject completed at least 28 days of study formula intake  $\geq$  90 kcal/kg/d and both blood samples obtained
- . If the study was not completed, and reason
- . Whether or not the subject received steroids (glucorticoids)
- . Investigator's evaluation of the study formula

The first and last dates study material was taken will be recorded.

#### 4.2.2.9 FINAL EVALUATION

At the final study visit (57 weeks postconceptual age) or earlier if the subject drops out, the Investigator will fill out a "Final Evaluation" Case Report Form. After reviewing the subject's records and discussion with the parents, the Investigator will indicate whether the subject:

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- (1) Completed feeding regiment and all study parameters (i.e., anthropometrics and visual acuity measured).
- (2) Did not complete feeding regimen.
- (3) Not completed and reason.

### 4.3 CLINICAL OBSERVATIONS

#### 4.3.1 PHYSICAL EXAMINATIONS

Subjects will have weight, length and head circumferences recorded at birth, weekly while hospitalized, then at 40, 48, and 57 weeks  $\pm$  4 days postconceptual age.

Body weight will be measured using an electronic balance or a double beam balance accurate to 10 g or  $\frac{1}{2}$  oz with non-detachable weights. During hospitalization, if more than one such balance is employed in the practice, either one balance should be designated the study balance and all study weights will be carried out on that balance for a particular subject, or the balances will be checked and certified to register the same weight throughout the range of weights expected. Outpatient weights will be obtained on a calibrated office scale.

Documentation indicating balance calibration of the outpatient balance carried out within 12 months of study initiation will be supplied to the Sponsor.

Length will be measured with the infant in recumbent position with the help of two examiners and a suitable measuring apparatus. One person holds the subject's head in contact with a fixed vertical headboard and a second person holds the subject's feet, toes pointing directly upward and, also applying gentle traction. The baby is measured from the headboard to the soles of the feet with a non-stretching tape measure.

Head circumference will be measured, employing a flexible, non-stretchable cloth or vinyl tape.

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4.3.2 VISUAL ACUITY BY FORCED CHOICE PREFERENTIAL  
LOOKING (FPL)

Visual acuity will be determined at 48 and 57 weeks  $\pm$  4 days postconceptual age according to procedures outlined in Appendix C.

4.3.3 LABORATORY TESTS

Blood will be drawn from preterm infants by heel prick or venipuncture when study formula is begun and terminated. An attempt will be made to draw blood at 48 weeks  $\pm$  4 days PCA from both term and preterm infants. Procedures for handling the blood are described in Appendix B.

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## 4.4 FLOW CHART

EVENT	PRETERM						TERM		
	Birth	Enteral Intake >50 kcal/kg/d	Termination of Study Formula †	Vislt 1 40 wks ± 4d PCA	Vislt 2 48 wks ± 4d PCA	Vislt 3 57 wks ± 4d PCA	Vislt 1 40 wks ± 4d PCA	Vislt 2 48 wks ± 4d PCA	Vislt 3 57 wks ± 4d PCA
Randomization		✓							
Study Formula		✓							
Enfamil w/iron			✓	✓	✓	✓			
Human Milk							✓	✓	✓
	Physical						Physical		
Weight	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Length	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Head Circumference	✓	✓*	✓	✓	✓	✓	✓	✓	✓
Blood Draw		✓	✓		✓			✓	
Visual Acuity Test					✓	✓		✓	✓
Illnesses				✓	✓	✓		✓	✓
Interim Assessment			✓						
Final Assessment							(when the subject discontinues or completes)		

✓ Medical problems related to or affecting formula consumption will be recorded when they occur.

\* Recorded daily and weekly during hospitalization.

† At hospital discharge or 28 days of study formula intake (after reaching 90 kcal/kg/d), whichever is later.

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## 5. CRITERIA FOR RESPONSE

Criteria for response will depend upon the following:

- Visual Acuity better than the control formula.
- Visual Acuity comparable to breastfed term infant.
- Red Blood Cell phosphatidyl ethanolamine DHA and ARA weight % greater than formula control group.
- Growth as measured by weight achieved at 48 and 57 weeks postconceptual age comparable to formula control group.

## 6. STATISTICS

### 6.1 RANDOMIZATION

If the subject meets the inclusion and exclusion criteria, randomization to one of three formula groups will take place. The randomization schedule will be provided by Mead Johnson Research Center. A separate randomization schedule will be provided for males and females.

### 6.2 SAMPLE SIZE

The primary parameter of interest is visual acuity as measured by the Forced Choice Preferential Looking (FPL). The minimal clinically relevant difference was determined to be 0.5 octave. A consultant in the field of visual acuity estimated the standard deviation to be 0.5 octave. This value was increased to .7 octave in case more variability was experienced in this study. Thirty-two subjects per group are needed to attain 80% power when testing at an alpha level of 0.05.

A sample size estimate of 50 per group was determined to achieve  $\alpha + 0.05$ ,  $\beta + 0.20$ , for weight of infants receiving study oil being greater than 400 gm below control at 48 weeks postconceptual age or 500 g below control at 57 weeks postconceptual age with a standard deviation of 800 g. It was therefore determined that 50 subjects per group will be used in the study.



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### 6.3 ANALYTICAL PLAN

Visual acuity data will be recorded in cycles per cm. These values will be converted to cycles per degree using the following formula:

$$\text{cycles/degree} = \frac{38 \times \text{cycles/cm}}{55}$$

A log transformation will be applied to the data prior to analysis. Analysis of variance techniques will be used to assess feeding regimen group differences in visual acuity. If the overall F test for feeding regimen is significant at an alpha level of 0.05, pairwise comparisons will be made at an alpha level of 0.05. If no significant differences are detected, then a post-study power analysis will be performed to demonstrate that the study had adequate power to detect the minimal clinically relevant difference.

Analysis of variance will be used to assess feeding regimen differences in phosphatidyl choline DHA and ARA levels and in phosphatidyl ethanolamine DHA and ARA levels at each time point. If the overall F test is significant at an alpha level of 0.05, then pairwise comparisons will be made at an alpha level of 0.05.

Analysis of variance will be used to assess feeding regimen differences in weight at 48 and 57 weeks postconceptual age. The statistical model will include terms for feeding regimen, study center, sex and all two-way interactions. Non-significant interactions will be removed from the final statistical model. Two one-sided tests will be performed comparing each experimental formula (EC) with the control formula (CF). The hypothesis to be tested is as follows:

$$H_0 = \text{Weight (CF)} \leq \text{Weight (EF)}.$$

The alternative hypothesis is as follows:

$$H_1 = \text{Weight (CF)} > \text{Weight (EF)}.$$

If  $H_0$  is rejected and the mean weight of the control formula exceeds that of the experimental formula by more than 400 mg at 48 weeks postconceptual age or by 500 g at 57 weeks postconceptual age then the conclusion is that the experimental formula does not exceed that of the experimental formula by more than 400 g at 48 weeks postconceptual age

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or by 500 mg at 57 weeks postconceptual age then the conclusion is that the experimental formula does provide adequate growth. If  $H_0$  is not rejected then a post-study power analysis will be performed to demonstrate that the study had adequate power to detect the above mentioned clinically relevant differences. If adequate power is achieved then the conclusion is that the experimental formula does provide adequate growth.

Fisher's exact test will be used to compare the proportion of subjects in each group with illness/symptoms of concern during the study. The analysis will be performed for each type of illness/symptom reported, with classification of investigator terms into similar terminology made as necessary.

## APPENDIX A

### NUTRIENT COMPOSITION OF FORMULAS

All study formulas are 24 kcal/fl oz and are identical in composition to marketed Enfamil Premature Formula except for the study oils employed. These oils are described in the protocol.

NUTRIENT	STUDY FORMULAS AMOUNT/100 kcal	ENFAMIL WITH Fe
Protein, g	3	2.2
Fat, g	5.1	5.6
Carbohydrate, g	11.1	10.3
Vitamin A IU	1250	310
Vitamin D IU	270	63
Vitamin E IU	6.3	2
Vitamin K mcg	8	8
Thiamine, mcg	200	78
Riboflavin, mcg	300	150
Vitamin B <sub>6</sub> , mcg	150	63
Vitamin B <sub>12</sub> , mcg	0.25	0.23
Niacin, mcg	4000	1250
Folic Acid, mcg	35	15.6
Pantothenate, mcg	1200	470
Biotin, mcg	4	2.3
Vitamin C, mg	20	8.1
Choline, mg	12	15.6
Inositol, mg	17	4.7
Calcium, mg	165	78
Phosphorus, mg	83	53
Magnesium, mg	6.3	7.8
Iron, mg	1.8	0.5
Zinc, mg	1.5	0.78
Manganese, mcg	6.3	15.6
Copper, mcg	125	94
Iodine, mcg	25	6
Sodium mg (mEq)	39 (1.7)	27 (1.17)
Potassium mg (Meq)	103 (2.6)	108 (2.8)
Chloride mg (Meq)	85 (2.4)	63 (1.77)

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## II

### FINAL STUDY REPORT

**Study Design:** This double-blind, parallel-group study (project 3338) was carried out in 16 neonatal centers (study numbers 9698-9709, 9712, 9723, 9743, and 9746) in North America. Three premature infant feedings were compared. Each had the same composition except for the incorporation of fungal and/or micro algal oils up to about 3% of the fat blend to provide the experimental levels of docosahexaenoic acid (DHA) and arachidonic acid (ARA). The control formula (C, Enfamil® Premature Formula) contained no DHA or ARA, the DHA formula (D) contained about 0.15% of energy as DHA (0.34% of fat), and the DHA+ARA formula (DA) contained about 0.14% of energy as DHA (0.33% of fat) and 0.27% of energy as ARA (0.60% of fat). The formulas were fed to 284 randomized infants weighing 846 to 1560 grams at birth for at least 28 days. Upon completion of study formula intake, they were given routine infant formula and followed through 4 months gestationally corrected age. A group of 90 exclusively human milk fed term infants were enrolled and followed to 4 months of age as a reference group (H).

**Study Objective and Statistical Analysis:** The primary objective of this study was to establish the safety of feeding D or DA to preterm infants during their initial hospitalization as measured 1) by growth, acceptance and tolerance while consuming the formula for at least 1 month and 2) by close monitoring and observation for a 4 to 5 month follow-up period (4-5 times the treatment period) while consuming unsupplemented routine term infant formula. The primary growth parameter selected was weight with evaluation of the proposition that weight on test formula was greater than or equal to weight on control formula. The one sided statistical test for an adverse effect on growth maximized the power to detect a difference should one be present. A two-sided test was used for all other parameters. A p-value of less than 0.05 was used to establish significance.

Secondary objectives of the study were 1) to evaluate the impact of fatty acid levels in erythrocyte phospholipids at the end of study feeding and 2) to determine if any effect on mean visual acuity greater than half an octave could be demonstrated at 2 and 4 months corrected age.

**Results:** Six infants were just outside the weight parameters and five infants just older than the less than 24 days chronological age parameter for enrollment in the study. In each case, judgement by the clinical or medical monitor was made to include them in the study prior to enrollment based on their homogeneity with other study infants in all other particulars, e.g., state of health, type of medical complications, and weight for gestational age. All these infants were included in the analysis of the study results.

The formula groups were comparable at enrollment (See table 1). Post-conceptual age, weight, length, and head circumference at enrollment did not differ among the groups.

All groups experienced comparable final study status (See table 2). Drop outs did not differ among the formula fed groups during hospitalization. There also were no differences in drop outs among the four groups at study completion.

Both formulas D and DA provide adequate growth when compared to formula C (See table 3, figure 1, and Appendix 1). Weight gain during hospitalization was no less on D or DA than on C, 33.3, 34.7, and 30.7 g/day, respectively. Furthermore, no less weight was achieved on D or DA than on C at 40, 48, and 57 weeks post-conceptual age (See table 4, figure 2, and Appendix 1); statistical power was greater than 0.89 to detect a clinically relevant decrease.

Post-hoc analysis reveals that infants on DA grew faster than infants receiving C and D (See table 5 and figure 1). This enhanced growth provided faster "premature infant catch-up" compared to C and D. Weight achieved by the DA group (3198 g) was higher than C (3075 g) and D (3051 g) at 40 weeks post-conceptual age but had not fully caught up to the term birth weight (3438 g) of group H (See table 4 and figure 2). This catch up trend continued through 48 to 57 weeks by which time the mean weight of group DA did not differ from group H while groups C and D remained significantly lower.

Length was not different among the formula groups either during hospitalization or the follow-up period, although the ordered sequence of mean lengths was the same as for the weights (See table 7 and figure 3). This is likely at least partially due to length being a less sensitive parameter of growth than weight. For the same reason, the mean lengths of group H infants were higher than that of all the premature infant groups at 40, 48 and 57 weeks post-conceptual age indicating slower catch up in this parameter.

Head circumference is the least sensitive parameter of growth and was not different among any of the four groups at any time measured except at 40 weeks postconceptual age (See table 8 and figure 4). At this time, as expected, the birth head circumference of group H was smaller than the formula fed premature infants possibly due to molding of labor and to insufficient time for adjustment to the extrauterine environment.

Visual acuity has reportedly been enhanced in studies where DHA supplemented formulas were fed to premature infants both in the hospital and continuing after discharge. In this study, visual acuity was measured about 3 months and then about 5 months after stopping study formula to determine whether a residual beneficial effect of at least half an octave might be observed. Although no difference in visual acuity was found among the formula groups at these times (See table 8 and figure 5), the acuity card method used, the length of study formula feeding, and/or the length of time not on study formula at the time of measurement may have precluded its detection. However, at 57 weeks post-conceptual age, the breast fed term infant group did have statistically higher visual acuity scores than the test formula groups. But even these differences were at most only 0.33 octave and were clinically insignificant (See figure 6). It is important to note that the breast fed infants continued to receive DHA and ARA during the 3-5 month follow-up period while the formula fed groups did not. Thus, this minor difference in performance was not unexpected based on previous study findings and on developmental differences between term and preterm infants even at the same gestational age.

Individual fatty acid levels were determined in the phosphatidylcholine and phosphatidylethanolamine fractions of red blood cells before formula feeding, at the conclusion of test formula feeding, and at 48 weeks post-conceptual age (See tables 9 and 10). The premature infant groups were comparable at the beginning of test formula feeding. At the conclusion of test

formula feeding, individual fatty acid levels varied among the groups. DHA and ARA were statistically significantly higher in the respectively supplemented groups. Other fatty acid levels reflected the impact of the supplementation. No clinically significant alterations in fatty acid levels or metabolism were identified. After discontinuing study formula and consuming a diet without DHA or ARA for about 3 months, no differences in fatty acid levels among formula fed groups were detectable, except for phosphatidylethanolamine levels of 18:2 (range 8.9-9.3%) and DHA (range 3.2-4.1%) which differences were not identified as being clinically significant. However, the breast fed group shows statistically significant differences in 13 fatty acid levels compared to the formula fed infants. These differences are undoubtedly due to the differences in fatty acid composition of human milk and the term formulas including the lack of DHA and ARA in the latter.

Preterm infant complications were similar in all groups (See table 11). Over 80% of all infants were ophthalmologically examined and over 90% had ultrasound evaluation of their heads. Specifically, the incidence and severity of retinopathy of prematurity (ROP or retrolental fibroplasia/RLF) and the incidence of intraventricular hemorrhage or its complications did not differ among formula groups. No feeding group related complications were identified.

Serious adverse experiences did not differ ( $p=0.93$ ) among the formula groups and were in the range of those expected in a premature infant population while on study formula: 6% in group C, 5% in group D, and 6% in group DA (See table 12). After the experimental formula phase, serious adverse experiences still did not differ among the preterm groups (See table 13): 13% in group C, 15% in group D, and 15% in group DA. However, the term infant breast fed group had significantly fewer serious adverse experiences (1%,  $p=0.002$ ) as expected. Two infants reportedly suffered sudden infant death syndrome (SIDS), one in group C and one in group D; there was no significant difference in this complication among all four groups.

**Conclusions:** We conclude that feeding 0.13% of calories as DHA from micro algal oil and feeding 0.13 % of calories as DHA from micro algal oil plus 0.26% of calories as ARA from fungal oil in the matrix of premature infant formula to premature infants during the period of their initial hospitalization prior to 40 weeks post conceptual age is safe. These micro algal and fungal oil supplements do not result in any adverse effect on growth, clinical complications, or untoward events. Furthermore, this study reveals that growth benefits accrue to premature infants fed Enfamil Premature Formula supplemented with DHA and ARA from these sources compared to unsupplemented formula or formula supplemented with only DHA. No measurable benefit on visual acuity was identified when infants were tested at about 3 and 5 months after the supplemented formula was discontinued (2 and 4 months corrected age). However, providing human milk levels of intake of long chain polyunsaturated acids are warranted because they are critical to brain development and foster enhanced catch-up growth during this early development period.

Table 1  
Birth Statistics of Premature Subjects

	n	Mean (std)	Range	p-value
Post-Conceptual Age (Weeks)				
Control	62	29.5 (1.7)	25 - 33	0.076
DHA	66	30.0 (1.4)	26 - 32	
DHA+ARA	66	29.7 (1.7)	26 - 34	
Birth Weight (g)				
Control	62	1233.1 (176.6)	846 - 1560	0.25
DHA	66	1272.8 (168.1)	900 - 1545	
DHA+ARA	66	1278.9 (177.6)	910 - 1535	
Birth Length (cm)				
Control	60	38.4 (2.3)	34 - 43.75	0.62
DHA	66	38.6 (2.2)	33 - 43.5	
DHA+ARA	66	38.7 (2.3)	33 - 44	
Birth Head Circumference (cm)				
Control	61	26.9 (1.5)	23.5 - 30.5	0.53
DHA	64	27.3 (2.1)	22 - 37	
DHA+ARA	65	27.2 (1.6)	23.5 - 30	

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Table 2  
Summary of Final Study Status

	Regimen				p-value
	Control	DHA	DHA+ARA	HM	
Immediate dropout, study formula never consumed		2	2		
Study Formula Phase *					
Completed	52 (84%)	59 (89%)	62 (94%)		0.20
Discontinued	10 (16%)	7 (11%)	4 (6%)		
Reason discontinued					
>96 cumulative hours NPO	3	1			
<28 days of intake $\geq$ 90 kcal/kg/day	3	3			
Complications unrelated to study formula	1				
NEC or other GI disease		1	1		
Formula intolerance			1		
Parents request	2	2	1		
Not off oxygen prior to discharge			1		
Protocol violation	1				
Term Formula Phase **					
Completed	45 (87%)	47 (80%)	53 (85%)	77 (86%)	0.74
Discontinued	7 (13%)	12 (20%)	9 (15%)	13 (14%)	

\*The CRFs for 9709-003 (DHA) and 9743-304 (DHA) were marked discontinued because the subjects met the study formula intake criteria for only 27 days. These subjects are counted completed here because subjects at other sites with similar intakes were marked completed.

\*\*Based on subjects who completed the Study Formula phase. During the Term Formula phase, subjects were fed marketed formula. Switching to a different marketed formula did not result in termination from the Term Formula phase.



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Table 3

Weight Growth Rate During Study Formula Phase							
Regimen	n	Least Square Mean	Standard Error	Comparison	Comparison p-value*	Study p-value	Gender p-value
Control	60	30.7	1.1	Control vs DHA	0.967	0.00	0.17
DHA	65	33.3	1.1	Control vs DHA+ARA	0.998		
DHA+ARA	66	34.7	1.1				0.87

\* One-sided test of the null hypothesis: Test Mean &gt;= Control Mean

Table 4  
Weight at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Comparison	Comparison p-value*	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	52	3075.3	67.9	Control vs DHA	0.388	0.59	0.45	1.00
	DHA	54	3051.4	66.8	Control vs DHA+ARA	0.931			
	DHA+ARA	59	3198.2	62.9	HM vs DHA	0.000			
	HM	90	3437.7	60.6	HM vs DHA+ARA	0.001			
48	Control	53	4711.0	94.6	HM vs Control	0.000	0.58	0.13	0.29
	DHA	51	4663.8	97.3	Control vs DHA	0.360			
	DHA+ARA	57	5039.1	93.0	Control vs DHA+ARA	0.995			
	HM	81	5181.5	85.9	HM vs DHA	0.000			
57	Control	47	6045.4	139.5	HM vs DHA+ARA	0.114	0.58	0.29	0.33
	DHA	49	5987.2	137.6	HM vs Control	0.000			
	DHA+ARA	55	6312.9	127.9	Control vs DHA	0.371			
	HM	76	6405.0	126.7	Control vs DHA+ARA	0.940			

\* One-sided test of the null hypothesis: Test Mean >= Control Mean

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Table 5  
Post-hoc Analysis of Weight

Time	Comparison	Two-sided p-value
Weight Gain During Study Formula Phase	C vs. DHA	0.067
	C vs. DHA+ARA	0.004
	DHA vs. DHA+ARA	0.30
Weight at 40 Weeks pca	C vs. DHA	0.78
	C vs. DHA+ARA	0.14
	DHA vs. DHA+ARA	0.074
	HM vs. DHA	<0.001
	HM vs. DHA+ARA	0.002
	HM vs. C	<0.001
Weight at 48 Weeks pca	C vs. DHA	0.72
	C vs. DHA+ARA	0.011
	DHA vs. DHA+ARA	0.004
	HM vs. DHA	<0.001
	HM vs. DHA+ARA	0.23
	HM vs. C	<0.001
Weight at 57 Weeks pca	C vs. DHA	0.74
	C vs. DHA+ARA	0.12
	DHA vs. DHA+ARA	0.057
	HM vs. DHA	0.010
	HM vs. DHA+ARA	0.56
	HM vs. C	0.028

Table 6  
Length at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	52	48.4	0.4	0.000	Control vs DHA	0.242	0.03	0.88	0.63
	DHA	54	47.8	0.4		Control vs DHA+ARA	0.233			
	DHA+ARA	58	49.0	0.4		HM vs DHA	0.000			
	HM	89	50.6	0.4		HM vs DHA+ARA	0.000			
48	Control	53	54.7	0.3	0.000	Control vs HM	0.000	0.00	0.14	0.52
	DHA	52	54.6	0.3		DHA vs DHA+ARA	0.824			
	DHA+ARA	57	55.5	0.3		Control vs DHA	0.079			
	HM	81	57.4	0.3		HM vs DHA	0.000			
57	Control	47	60.7	0.4	0.000	Control vs DHA	0.615	0.00	0.02	0.84
	DHA	49	60.5	0.4		Control vs DHA+ARA	0.236			
	DHA+ARA	54	61.3	0.3		HM vs DHA	0.000			
	HM	76	62.4	0.3		HM vs DHA+ARA	0.006			
						Control vs HM	0.000			
						DHA vs DHA+ARA	0.087			

Table 7

Head Circumference at 40, 48, and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Least Square Mean	Standard Error	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value	Gender p-value	Gender-by-Regimen p-value
40	Control	51	35.4	0.2	0.000	Control vs DHA	0.931	0.91	0.00	0.38
	DHA	53	35.4	0.2		Control vs DHA+ARA	0.900			
	DHA+ARA	58	35.5	0.2		HH vs DHA	0.000			
	HH	85	34.5	0.2		HH vs DHA+ARA	0.000			
48	Control	52	39.1	0.2	0.983	Control vs HH	0.000	0.81	0.00	1.00
	DHA	51	39.0	0.2		DHA vs DHA+ARA	0.829			
	DHA+ARA	56	39.0	0.2						
	HH	81	39.0	0.1						
57	Control	47	41.9	0.2	0.689			0.64	0.00	0.85
	DHA	49	41.6	0.2						
	DHA+ARA	53	41.7	0.2						
	HH	76	41.7	0.2						

Table 8  
Visual Acuity at 48 and 57 Weeks Post-Conceptual Age

Weeks Post-Conceptual Age	Regimen	n	Geometric mean (cycles/deg)	Least Square Mean (log base2 cycles/deg)	Standard Error (octaves)	Regimen p-value	Pairwise Comparison	Pairwise p-value	Study p-value
48	Control	51	1.72	0.78	0.10	0.950			0.000
	DHA	50	1.80	0.85	0.10				
	DHA+ARA	57	1.72	0.78	0.09				
	IH	81	1.75	0.81	0.09				
57	Control	46	3.47	1.79	0.08	0.004	Control vs DHA	0.697	0.000
	DHA	47	3.37	1.75	0.08		Control vs DHA+ARA	0.071	
	DHA+ARA	55	3.06	1.61	0.07		IH vs DHA	0.042	
	IH	77	3.85	1.94	0.07		IH vs DHA+ARA	0.000	
							Control vs IH	0.113	
							DHA vs DHA+ARA	0.158	

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Table 9  
Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	12:0	Control	52	0.081	0.019	0.036	0.762		
		DHA	58	0.066	0.013	0.030			
		DHA+ARA	61	0.057	0.009	0.031			
Study Form Initiation	14:0	Control	52	0.623	0.036	0.599	0.559		
		DHA	58	0.663	0.031	0.686			
		DHA+ARA	61	0.661	0.031	0.656			
Study Form Initiation	14:1	Control	52	0.045	0.009	0.021	0.165		
		DHA	58	0.026	0.005	0.016			
		DHA+ARA	61	0.035	0.006	0.018			
Study Form Initiation	16:0	Control	52	36.706	0.540	36.594	0.884		
		DHA	58	36.363	0.462	35.578			
		DHA+ARA	61	36.877	0.445	35.987			
Study Form Initiation	16:1	Control	52	0.940	0.049	0.845	0.441		
		DHA	58	0.981	0.050	0.976			
		DHA+ARA	61	1.094	0.064	0.931			
Study Form Initiation	18:0	Control	52	11.660	0.243	11.468	0.243		
		DHA	58	11.402	0.238	11.201			
		DHA+ARA	61	11.016	0.192	11.174			
Study Form Initiation	18:1	Control	52	17.053	0.298	17.308	0.679		
		DHA	58	17.219	0.391	16.935			
		DHA+ARA	61	17.256	0.271	16.988			
Study Form Initiation	18:2	Control	52	18.614	0.525	18.952	0.830		
		DHA	58	18.631	0.505	19.603			
		DHA+ARA	61	18.573	0.466	18.824			
Study Form Initiation	18:3n6	Control	52	0.120	0.008	0.116	0.034	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.196 0.010 0.176
		DHA	58	0.136	0.008	0.130			
		DHA+ARA	61	0.150	0.009	0.134			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	20:0	Control	52	0.399	0.050	0.224	0.647		
		DHA	58	0.337	0.035	0.236			
		DHA+ARA	61	0.310	0.037	0.188			
Study Form Initiation	18:3n3	Control	52	0.315	0.033	0.246	0.234		
		DHA	58	0.257	0.014	0.246			
		DHA+ARA	61	0.233	0.010	0.216			
Study Form Initiation	20:1	Control	52	0.287	0.020	0.262	0.723		
		DHA	58	0.287	0.015	0.281			
		DHA+ARA	61	0.268	0.011	0.269			
Study Form Initiation	18:4	Control	52	0.017	0.003	0.000	0.290		
		DHA	58	0.025	0.004	0.017			
		DHA+ARA	61	0.017	0.003	0.008			
Study Form Initiation	20:2n6	Control	52	0.632	0.025	0.632	0.673		
		DHA	58	0.628	0.025	0.640			
		DHA+ARA	61	0.602	0.021	0.614			
Study Form Initiation	20:3n6	Control	52	2.144	0.098	2.096	0.507		
		DHA	58	2.208	0.080	2.296			
		DHA+ARA	61	2.218	0.074	2.135			
Study Form Initiation	20:4n6	Control	52	7.657	0.262	8.124	0.819		
		DHA	58	8.164	0.347	7.876			
		DHA+ARA	61	8.090	0.310	8.207			
Study Form Initiation	22:1	Control	52	0.106	0.010	0.105	0.155		
		DHA	58	0.127	0.010	0.130			
		DHA+ARA	61	0.126	0.010	0.139			
Study Form Initiation	20:5n3	Control	52	0.351	0.057	0.298	0.911		
		DHA	58	0.322	0.015	0.302			
		DHA+ARA	61	0.321	0.015	0.329			



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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	22:4n6	Control	52	0.578	0.144	0.423	0.331		
		DHA	58	0.493	0.030	0.481			
		DHA+ARA	61	0.443	0.021	0.425			
Study Form Initiation	24:1	Control	52	0.208	0.054	0.075	0.665		
		DHA	58	0.115	0.019	0.084			
		DHA+ARA	61	0.180	0.056	0.096			
Study Form Initiation	22:5n6	Control	52	0.266	0.020	0.232	0.923		
		DHA	58	0.259	0.017	0.239			
		DHA+ARA	61	0.265	0.018	0.256			
Study Form Initiation	22:4n3	Control	52	0.000	0.000	0.000	0.199		
		DHA	58	0.001	0.001	0.000			
		DHA+ARA	61	0.002	0.001	0.000			
Study Form Initiation	22:5n3	Control	52	0.213	0.019	0.203	0.885		
		DHA	58	0.215	0.013	0.195			
		DHA+ARA	61	0.203	0.010	0.193			
Study Form Initiation	22:6n3	Control	52	0.984	0.051	1.000	0.858		
		DHA	58	1.075	0.053	1.034			
		DHA+ARA	61	1.006	0.050	0.970			

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Table 9  
Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	12:0	Control	53	0.100	0.026	0.035	0.843		
		DHA	56	0.111	0.042	0.031			
		DHA+ARA	59	0.064	0.012	0.032			
Study Form Termination	14:0	Control	53	0.808	0.039	0.806	0.834		
		DHA	56	0.781	0.035	0.783			
		DHA+ARA	59	0.755	0.036	0.758			
Study Form Termination	14:1	Control	53	0.047	0.008	0.033	0.155		
		DHA	56	0.036	0.009	0.015			
		DHA+ARA	59	0.036	0.007	0.018			
Study Form Termination	16:0	Control	53	35.837	0.512	34.798	0.767		
		DHA	56	35.560	0.595	34.841			
		DHA+ARA	59	35.069	0.584	33.890			
Study Form Termination	16:1	Control	53	0.566	0.026	0.526	0.013	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.118 0.003 0.152
		DHA	56	0.594	0.042	0.475			
		DHA+ARA	59	0.526	0.029	0.472			
Study Form Termination	18:0	Control	53	13.972	0.261	14.197	0.886		
		DHA	56	14.065	0.237	13.867			
		DHA+ARA	59	14.341	0.253	14.108			
Study Form Termination	18:1	Control	53	14.456	0.277	14.291	0.686		
		DHA	56	14.116	0.272	13.998			
		DHA+ARA	59	14.344	0.380	14.218			
Study Form Termination	18:2	Control	53	21.673	0.340	21.506	0.001	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.600 0.005 0.001
		DHA	56	22.045	0.457	22.517			
		DHA+ARA	59	19.899	0.337	20.662			
Study Form Termination	18:3n6	Control	53	0.080	0.006	0.074	0.527		
		DHA	56	0.088	0.009	0.076			
		DHA+ARA	59	0.087	0.013	0.066			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	20:0	Control	53	0.504	0.050	0.392	0.424		
		DHA	56	0.472	0.053	0.281			
		DHA+ARA	59	0.430	0.049	0.251			
Study Form Termination	18:3n3	Control	53	0.321	0.020	0.283	0.031	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.503 0.068 0.011
		DHA	56	0.335	0.030	0.285			
		DHA+ARA	59	0.273	0.009	0.256			
Study Form Termination	20:1	Control	53	0.318	0.014	0.302	0.149		
		DHA	56	0.300	0.013	0.283			
		DHA+ARA	59	0.307	0.013	0.283			
Study Form Termination	18:4	Control	53	0.022	0.004	0.015	0.672		
		DHA	56	0.022	0.003	0.018			
		DHA+ARA	59	0.014	0.002	0.008			
Study Form Termination	20:2n6	Control	53	0.893	0.026	0.910	0.051		
		DHA	56	0.880	0.023	0.873			
		DHA+ARA	59	0.824	0.022	0.821			
Study Form Termination	20:3n6	Control	53	2.032	0.073	2.091	0.208		
		DHA	56	2.017	0.070	2.043			
		DHA+ARA	59	1.908	0.064	1.904			
Study Form Termination	20:4n6	Control	53	6.046	0.240	6.029	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.097 0.000 0.000
		DHA	56	5.774	0.220	5.892			
		DHA+ARA	59	8.465	0.255	8.891			
Study Form Termination	22:1	Control	53	0.117	0.010	0.125	0.946		
		DHA	56	0.110	0.009	0.114			
		DHA+ARA	59	0.115	0.011	0.104			
Study Form Termination	20:5n3	Control	53	0.214	0.022	0.189	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.004 0.108 0.000
		DHA	56	0.246	0.012	0.233			
		DHA+ARA	59	0.186	0.014	0.169			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	22:4n6	Control	53	0.484	0.048	0.390	0.093		
		DHA	56	0.489	0.061	0.426			
		DHA+ARA	59	0.496	0.027	0.487			
Study Form Termination	24:1	Control	53	0.127	0.039	0.062	0.303		
		DHA	56	0.143	0.036	0.086			
		DHA+ARA	59	0.177	0.040	0.089			
Study Form Termination	22:5n6	Control	53	0.181	0.013	0.163	0.006	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.005 0.895 0.006
		DHA	56	0.145	0.011	0.133			
		DHA+ARA	59	0.172	0.009	0.165			
Study Form Termination	22:4n3	Control	53	0.001	0.001	0.000	0.359		
		DHA	56	0.001	0.001	0.000			
		DHA+ARA	59	0.003	0.002	0.000			
Study Form Termination	22:5n3	Control	53	0.306	0.019	0.289	0.221		
		DHA	56	0.293	0.026	0.260			
		DHA+ARA	59	0.265	0.013	0.255			
Study Form Termination	22:6n3	Control	53	0.895	0.072	0.812	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.000 0.000 0.141
		DHA	56	1.380	0.063	1.352			
		DHA+ARA	59	1.244	0.049	1.259			

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	12:0	Control	37	0.032	0.005	0.026	0.729		
		DHA	32	0.028	0.006	0.016			
		DHA+ARA	38	0.026	0.004	0.021			
		HM	56	0.059	0.016	0.020			
48 Weeks PCA	14:0	Control	37	0.402	0.039	0.331	0.943		
		DHA	32	0.353	0.032	0.324			
		DHA+ARA	38	0.353	0.024	0.328			
		HM	56	0.381	0.026	0.335			
48 Weeks PCA	14:1	Control	37	0.025	0.006	0.013	0.448		
		DHA	32	0.026	0.007	0.011			
		DHA+ARA	38	0.026	0.006	0.015			
		HM	56	0.024	0.003	0.020			
48 Weeks PCA	16:0	Control	37	34.627	0.577	34.319	0.000	Control vs DHA Control vs DHA+ARA HM vs DHA HM vs DHA+ARA Control vs HM DHA vs DHA+ARA	0.527 0.593 0.000 0.000 0.000 0.906
		DHA	32	35.272	0.689	34.473			
		DHA+ARA	38	34.802	0.506	34.165			
		HM	56	33.037	0.506	32.228			
48 Weeks PCA	16:1	Control	37	0.435	0.043	0.338	0.000	Control vs DHA Control vs DHA+ARA HM vs DHA HM vs DHA+ARA Control vs HM DHA vs DHA+ARA	0.524 0.467 0.000 0.006 0.000 0.183
		DHA	32	0.380	0.023	0.352			
		DHA+ARA	38	0.395	0.024	0.368			
		HM	56	0.507	0.020	0.473			

Table 9

Red Blood Cell Phosphatidylcholine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:0	Control	37	13.016	0.313	12.759	0.000	Control vs DHA	0.760
		DHA	32	12.944	0.249	12.786		Control vs DHA+ARA	0.889
		DHA+ARA	38	12.804	0.235	12.793		HM vs DHA	0.000
		HM	56	14.583	0.287	14.729		HM vs DHA+ARA	0.000
48 Weeks PCA	18:1	Control	37	17.894	0.453	18.636	0.256	Control vs HM	0.000
		DHA	32	17.766	0.429	18.492		DHA vs DHA+ARA	0.661
		DHA+ARA	38	17.850	0.289	18.227			
		HM	56	18.662	0.305	18.727			
48 Weeks PCA	18:2	Control	37	23.469	0.518	23.552	0.000	Control vs DHA	0.840
		DHA	32	23.538	0.516	23.717		Control vs DHA+ARA	0.527
		DHA+ARA	38	23.738	0.422	23.839		HM vs DHA	0.000
		HM	56	18.650	0.344	18.482		HM vs DHA+ARA	0.000
48 Weeks PCA	18:3n6	Control	37	0.071	0.008	0.061	0.002	Control vs HM	0.000
		DHA	32	0.069	0.005	0.067		DHA vs DHA+ARA	0.685
		DHA+ARA	38	0.069	0.006	0.062		Control vs DHA	0.950
		HM	56	0.042	0.004	0.039		Control vs DHA+ARA	0.774
48 Weeks PCA	20:0	Control	37	0.348	0.075	0.197	0.785	HM vs DHA	0.004
		DHA	32	0.339	0.061	0.206		HM vs DHA+ARA	0.001
		DHA+ARA	38	0.304	0.061	0.172		Control vs HM	0.003
		HM	56	0.409	0.044	0.215		DHA vs DHA+ARA	0.831

Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:3n3	Control	37	0.222	0.019	0.182	0.001	Control vs DHA	0.812
		DHA	32	0.211	0.015	0.182		Control vs DHA+ARA	0.918
		DHA+ARA	38	0.203	0.010	0.190		HM vs DHA	0.001
		HM	56	0.182	0.022	0.120		HM vs DHA+ARA	0.002
								Control vs HM	0.001
								DHA vs DHA+ARA	0.737
48 Weeks PCA	20:1	Control	37	0.418	0.019	0.420	0.000	Control vs DHA	0.579
		DHA	32	0.406	0.025	0.435		Control vs DHA+ARA	0.588
		DHA+ARA	38	0.382	0.016	0.375		HM vs DHA	0.001
		HM	56	0.311	0.014	0.309		HM vs DHA+ARA	0.001
								Control vs HM	0.000
								DHA vs DHA+ARA	0.974
48 Weeks PCA	18:4	Control	37	0.018	0.005	0.000	0.010	Control vs DHA	0.822
		DHA	32	0.016	0.004	0.000		Control vs DHA+ARA	0.161
		DHA+ARA	38	0.007	0.002	0.000		HM vs DHA	0.039
		HM	56	0.024	0.004	0.015		HM vs DHA+ARA	0.001
								Control vs HM	0.054
								DHA vs DHA+ARA	0.262
48 Weeks PCA	20:2n6	Control	37	0.543	0.023	0.537	0.629	Control vs DHA	
		DHA	32	0.557	0.032	0.543		Control vs DHA+ARA	
		DHA+ARA	38	0.636	0.053	0.550		HM vs DHA	
		HM	56	0.560	0.014	0.531		HM vs DHA+ARA	
								Control vs HM	
								DHA vs DHA+ARA	
48 Weeks PCA	20:3n6	Control	37	1.709	0.086	1.741	0.000	Control vs DHA	0.610
		DHA	32	1.702	0.073	1.684		Control vs DHA+ARA	0.735
		DHA+ARA	38	1.844	0.090	1.717		HM vs DHA	0.000
		HM	56	2.265	0.086	2.166		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.405

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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	20:4n6	Control	37	4.738	0.255	4.736	0.000	Control vs DHA	0.508
		DHA	32	4.475	0.196	4.499		Control vs DHA+ARA	0.805
		DHA+ARA	38	4.550	0.185	4.746		HM vs DHA	0.000
		HM	56	7.408	0.250	7.666		HM vs DHA+ARA	0.000
48 Weeks PCA	22:1	Control	37	0.166	0.036	0.131	0.664	Control vs HM	0.000
		DHA	32	0.116	0.014	0.118		DHA vs DHA+ARA	0.672
		DHA+ARA	38	0.131	0.024	0.105			
		HM	56	0.160	0.030	0.104			
48 Weeks PCA	20:5n3	Control	37	0.102	0.015	0.077	0.000	Control vs DHA	0.633
		DHA	32	0.084	0.006	0.083		Control vs DHA+ARA	0.086
		DHA+ARA	38	0.099	0.009	0.078		HM vs DHA	0.000
		HM	56	0.138	0.009	0.123		HM vs DHA+ARA	0.000
48 Weeks PCA	22:4n6	Control	37	0.426	0.059	0.373	0.244	Control vs HM	0.000
		DHA	32	0.382	0.029	0.417		DHA vs DHA+ARA	0.239
		DHA+ARA	38	0.440	0.054	0.384			
		HM	56	0.406	0.022	0.377			
48 Weeks PCA	24:1	Control	37	0.247	0.070	0.112	0.000	Control vs DHA	0.337
		DHA	32	0.210	0.062	0.116		Control vs DHA+ARA	0.247
		DHA+ARA	38	0.179	0.055	0.108		HM vs DHA	0.000
		HM	56	0.115	0.020	0.079		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.878



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Table 9

## Red Blood Cell Phosphatidylcholine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	22:5n6	Control	37	0.210	0.016	0.212	0.000	Control vs DHA	0.505
		DHA	32	0.189	0.012	0.186		Control vs DHA+ARA	0.647
		DHA+ARA	38	0.231	0.022	0.198		HM vs DHA	0.000
		HM	56	0.264	0.016	0.265		HM vs DHA+ARA	0.001
48 Weeks PCA	22:4n3	Control	37	0.000	0.000	0.000	1.000	Control vs HM	0.000
		DHA	32	0.000	0.000	0.000		DHA vs DHA+ARA	0.270
		DHA+ARA	38	0.000	0.000	0.000			
		HM	56	0.000	0.000	0.000			
48 Weeks PCA	22:5n3	Control	37	0.286	0.029	0.260	0.000	Control vs DHA	0.598
		DHA	32	0.253	0.017	0.251		Control vs DHA+ARA	0.759
		DHA+ARA	38	0.268	0.026	0.256		HM vs DHA	0.000
		HM	56	0.339	0.018	0.314		HM vs DHA+ARA	0.000
48 Weeks PCA	22:6n3	Control	37	0.595	0.047	0.569	0.000	Control vs HM	0.817
		DHA	32	0.685	0.048	0.676		DHA vs DHA+ARA	0.111
		DHA+ARA	38	0.662	0.043	0.663		Control vs DHA	0.052
		HM	56	1.475	0.081	1.333		HM vs DHA	0.000
								HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.776

Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	12:0	Control	52	0.069	0.015	0.022	0.546		
		DHA	57	0.075	0.013	0.033			
		DHA+ARA	61	0.063	0.010	0.039			
Study Form Initiation	14:0	Control	52	0.307	0.038	0.220	0.792		
		DHA	57	0.278	0.025	0.206			
		DHA+ARA	61	0.277	0.021	0.246			
Study Form Initiation	14:1	Control	52	0.080	0.015	0.032	0.181		
		DHA	57	0.061	0.012	0.028			
		DHA+ARA	61	0.062	0.009	0.050			
Study Form Initiation	16:0	Control	52	20.021	0.736	17.945	0.967		
		DHA	57	19.847	0.622	19.295			
		DHA+ARA	61	19.796	0.451	19.035			
Study Form Initiation	16:1	Control	52	0.731	0.035	0.698	0.337		
		DHA	57	0.769	0.034	0.746			
		DHA+ARA	61	0.836	0.035	0.837			
Study Form Initiation	18:0	Control	52	8.857	0.329	8.469	0.142		
		DHA	57	8.434	0.227	8.308			
		DHA+ARA	61	8.201	0.215	7.904			
Study Form Initiation	18:1	Control	52	16.450	0.301	16.698	0.412		
		DHA	57	16.208	0.326	16.308			
		DHA+ARA	61	16.415	0.375	16.001			
Study Form Initiation	18:2	Control	52	6.615	0.253	6.682	0.773		
		DHA	57	6.336	0.280	6.346			
		DHA+ARA	61	6.175	0.294	5.682			
Study Form Initiation	18:3n6	Control	52	0.165	0.018	0.145	0.040	Control vs DHA	0.373
		DHA	57	0.190	0.019	0.152		Control vs DHA+ARA	0.013
		DHA+ARA	61	0.192	0.016	0.169		DHA vs DHA+ARA	0.101

Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	20:0	Control	52	0.372	0.043	0.291	0.151		
		DHA	57	0.314	0.030	0.244			
		DHA+ARA	61	0.259	0.024	0.186			
Study Form Initiation	18:3n3	Control	52	0.305	0.023	0.261	0.641		
		DHA	57	0.269	0.018	0.249			
		DHA+ARA	61	0.257	0.016	0.225			
Study Form Initiation	20:1	Control	52	0.573	0.036	0.517	0.395		
		DHA	57	0.615	0.034	0.555			
		DHA+ARA	61	0.571	0.027	0.544			
Study Form Initiation	18:4	Control	52	0.025	0.005	0.000	0.371		
		DHA	57	0.031	0.004	0.025			
		DHA+ARA	61	0.030	0.007	0.021			
Study Form Initiation	20:2n6	Control	52	0.479	0.023	0.480	0.706		
		DHA	57	0.463	0.024	0.437			
		DHA+ARA	61	0.443	0.028	0.427			
Study Form Initiation	20:3n6	Control	52	1.843	0.072	1.829	0.099		
		DHA	57	1.965	0.077	1.820			
		DHA+ARA	61	1.973	0.064	1.911			
Study Form Initiation	20:4n6	Control	52	25.817	0.618	26.820	0.353		
		DHA	57	26.475	0.611	27.376			
		DHA+ARA	61	26.747	0.645	27.708			
Study Form Initiation	22:1	Control	52	0.150	0.017	0.138	0.572		
		DHA	57	0.167	0.015	0.151			
		DHA+ARA	61	0.168	0.017	0.141			
Study Form Initiation	20:5n3	Control	52	0.378	0.024	0.357	0.997		
		DHA	57	0.384	0.024	0.370			
		DHA+ARA	61	0.366	0.022	0.335			

Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Initiation	22:4n6	Control	52	7.290	0.182	7.402	0.875		
		DHA	57	7.431	0.186	7.638			
		DHA+ARA	61	7.456	0.167	7.270			
Study Form Initiation	24:1	Control	52	0.100	0.028	0.041	0.068		
		DHA	57	0.059	0.009	0.031			
		DHA+ARA	61	0.072	0.010	0.047			
Study Form Initiation	22:5n6	Control	52	1.757	0.083	1.782	0.555		
		DHA	57	1.809	0.070	1.857			
		DHA+ARA	61	1.851	0.075	1.775			
Study Form Initiation	22:4n3	Control	52	0.001	0.001	0.000	0.257		
		DHA	57	0.001	0.001	0.000			
		DHA+ARA	61	0.005	0.002	0.000			
Study Form Initiation	22:5n3	Control	52	1.496	0.109	1.308	0.195		
		DHA	57	1.375	0.109	0.988			
		DHA+ARA	61	1.380	0.097	1.041			
Study Form Initiation	22:6n3	Control	52	6.119	0.200	6.381	0.375		
		DHA	57	6.444	0.185	6.468			
		DHA+ARA	61	6.407	0.220	6.579			

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Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	12:0	Control	53	0.093	0.018	0.033	0.630		
		DHA	55	0.093	0.019	0.036			
		DHA+ARA	58	0.067	0.012	0.035			
Study Form Termination	14:0	Control	53	0.360	0.031	0.279	0.782		
		DHA	55	0.380	0.039	0.265			
		DHA+ARA	58	0.348	0.030	0.256			
Study Form Termination	14:1	Control	53	0.086	0.020	0.041	0.592		
		DHA	55	0.066	0.013	0.000			
		DHA+ARA	58	0.066	0.011	0.043			
Study Form Termination	16:0	Control	53	19.326	0.673	17.617	0.560		
		DHA	55	19.062	0.614	17.556			
		DHA+ARA	58	18.357	0.467	17.568			
Study Form Termination	16:1	Control	53	0.511	0.034	0.476	0.604		
		DHA	55	0.579	0.045	0.509			
		DHA+ARA	58	0.618	0.049	0.555			
Study Form Termination	18:0	Control	53	9.614	0.266	9.406	0.024	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.130 0.006 0.219
		DHA	55	9.173	0.208	8.818			
		DHA+ARA	58	8.961	0.242	8.697			
Study Form Termination	18:1	Control	53	14.763	0.437	14.695	0.333		
		DHA	55	15.177	0.299	14.927			
		DHA+ARA	58	14.814	0.330	14.499			
Study Form Termination	18:2	Control	53	9.405	0.192	9.359	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.908 0.000 0.000
		DHA	55	9.180	0.207	9.188			
		DHA+ARA	58	7.756	0.141	7.586			
Study Form Termination	18:3n6	Control	53	0.169	0.012	0.163	0.160		
		DHA	55	0.187	0.017	0.157			
		DHA+ARA	58	0.198	0.018	0.161			

Table 10  
Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	20:0	Control	53	0.404	0.044	0.278	0.146		
		DHA	55	0.336	0.037	0.208			
		DHA+ARA	58	0.288	0.029	0.208			
Study Form Termination	18:3n3	Control	53	0.382	0.017	0.364	0.134		
		DHA	55	0.368	0.016	0.354			
		DHA+ARA	58	0.329	0.015	0.305			
Study Form Termination	20:1	Control	53	0.553	0.029	0.526	0.164		
		DHA	55	0.579	0.028	0.537			
		DHA+ARA	58	0.507	0.025	0.483			
Study Form Termination	18:4	Control	53	0.042	0.010	0.018	0.108		
		DHA	55	0.026	0.005	0.019			
		DHA+ARA	58	0.022	0.004	0.000			
Study Form Termination	20:2n6	Control	53	0.754	0.029	0.765	0.068		
		DHA	55	0.774	0.030	0.750			
		DHA+ARA	58	0.654	0.026	0.663			
Study Form Termination	20:3n6	Control	53	2.253	0.111	2.073	0.203		
		DHA	55	2.295	0.094	2.206			
		DHA+ARA	58	2.066	0.073	1.992			
Study Form Termination	20:4n6	Control	53	24.279	0.527	25.132	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.119 0.000 0.000
		DHA	55	23.464	0.520	24.038			
		DHA+ARA	58	26.760	0.437	27.372			
Study Form Termination	22:1	Control	53	0.149	0.019	0.122	0.229		
		DHA	55	0.176	0.016	0.169			
		DHA+ARA	58	0.146	0.012	0.130			
Study Form Termination	20:5n3	Control	53	0.519	0.020	0.493	0.000	Control vs DHA Control vs DHA+ARA DHA vs DHA+ARA	0.286 0.000 0.000
		DHA	55	0.563	0.025	0.575			
		DHA+ARA	58	0.411	0.015	0.415			

Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
Study Form Termination	22:4n6	Control	53	7.309	0.208	7.656	0.007	Control vs DHA	0.025
		DHA	55	7.135	0.154	6.885		Control vs DHA+ARA	0.461
		DHA+ARA	58	7.592	0.155	7.635		DHA vs DHA+ARA	0.002
Study Form Termination	24:1	Control	53	0.092	0.023	0.038	0.294		
		DHA	55	0.056	0.009	0.042			
		DHA+ARA	58	0.062	0.008	0.041			
Study Form Termination	22:5n6	Control	53	1.444	0.064	1.423	0.010	Control vs DHA	0.003
		DHA	55	1.231	0.034	1.213		Control vs DHA+ARA	0.255
		DHA+ARA	58	1.347	0.040	1.330		DHA vs DHA+ARA	0.050
Study Form Termination	22:4n3	Control	53	0.000	0.000	0.000	0.137		
		DHA	55	0.004	0.002	0.000			
		DHA+ARA	58	0.004	0.002	0.000			
Study Form Termination	22:5n3	Control	53	2.694	0.110	2.839	0.003	Control vs DHA	0.004
		DHA	55	2.334	0.091	2.400		Control vs DHA+ARA	0.002
		DHA+ARA	58	2.237	0.069	2.269		DHA vs DHA+ARA	0.943
Study Form Termination	22:6n3	Control	53	4.798	0.151	4.815	0.000	Control vs DHA	0.000
		DHA	55	6.762	0.183	7.043		Control vs DHA+ARA	0.000
		DHA+ARA	58	6.389	0.150	6.498		DHA vs DHA+ARA	0.027

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Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	12:0	Control	37	0.053	0.019	0.024	0.587		
		DHA	32	0.054	0.016	0.019			
		DHA+ARA	38	0.047	0.014	0.018			
		HM	56	0.045	0.011	0.023			
48 Weeks PCA	14:0	Control	37	0.243	0.030	0.169	0.598		
		DHA	32	0.251	0.041	0.162			
		DHA+ARA	38	0.235	0.025	0.188			
		HM	56	0.230	0.016	0.210			
48 Weeks PCA	14:1	Control	37	0.080	0.017	0.037	0.092		
		DHA	32	0.055	0.017	0.000			
		DHA+ARA	38	0.078	0.019	0.044			
		HM	56	0.053	0.011	0.021			
48 Weeks PCA	16:0	Control	37	17.319	0.595	16.314	0.177		
		DHA	32	17.101	0.729	15.692			
		DHA+ARA	38	17.225	0.538	16.997			
		HM	56	18.138	0.395	17.607			
48 Weeks PCA	16:1	Control	37	0.440	0.050	0.349	0.000	Control vs DHA	0.601
		DHA	32	0.390	0.035	0.336		Control vs DHA+ARA	0.524
		DHA+ARA	38	0.390	0.022	0.376		HM vs DHA	0.000
		HM	56	0.596	0.027	0.562		HM vs DHA+ARA	0.000
								Control vs HM	0.001
								DHA vs DHA+ARA	0.928





Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	18:3n3	Control	37	0.291	0.025	0.225	0.001	Control vs DHA	0.559
		DHA	32	0.270	0.017	0.262		Control vs DHA+ARA	0.848
		DHA+ARA	38	0.265	0.015	0.245		HM vs DHA	0.008
		HM	56	0.226	0.020	0.169		HM vs DHA+ARA	0.002
								Control vs HM	0.001
								DHA vs DHA+ARA	0.689
48 Weeks PCA	20:1	Control	37	0.715	0.031	0.648	0.000	Control vs DHA	0.339
		DHA	32	0.772	0.032	0.782		Control vs DHA+ARA	0.512
		DHA+ARA	38	0.936	0.188	0.738		HM vs DHA	0.000
		HM	56	0.533	0.024	0.492		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.115
48 Weeks PCA	18:4	Control	37	0.017	0.005	0.003	0.057		
		DHA	32	0.017	0.005	0.000			
		DHA+ARA	38	0.023	0.006	0.000			
		HM	56	0.027	0.004	0.019			
48 Weeks PCA	20:2n6	Control	37	0.672	0.035	0.698	0.000	Control vs DHA	0.543
		DHA	32	0.668	0.026	0.684		Control vs DHA+ARA	0.532
		DHA+ARA	38	0.715	0.032	0.689		HM vs DHA	0.000
		HM	56	0.444	0.016	0.412		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.995
48 Weeks PCA	20:3n6	Control	37	2.138	0.099	1.999	0.012	Control vs DHA	0.896
		DHA	32	2.165	0.100	2.045		Control vs DHA+ARA	0.935
		DHA+ARA	38	2.172	0.114	2.132		HM vs DHA	0.015
		HM	56	1.715	0.053	1.637		HM vs DHA+ARA	0.006
								Control vs HM	0.007
								DHA vs DHA+ARA	0.835

Table 10

Red Blood Cell Phosphatidylethanolamine Fatty Acids									
Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	20:4n6	Control	37	24.508	0.536	24.774	0.950		
		DHA	32	24.428	0.491	25.206			
		DHA+ARA	38	24.788	0.429	25.122			
		HM	56	24.625	0.384	25.189			
48 Weeks PCA	22:1	Control	37	0.168	0.016	0.172	0.121		
		DHA	32	0.189	0.022	0.188			
		DHA+ARA	38	0.154	0.022	0.133			
		HM	56	0.148	0.013	0.134			
48 Weeks PCA	20:5n3	Control	37	0.382	0.026	0.368	0.497		
		DHA	32	0.369	0.015	0.377			
		DHA+ARA	38	0.347	0.011	0.347			
		HM	56	0.384	0.016	0.360			
48 Weeks PCA	22:4n6	Control	37	8.580	0.267	8.761	0.001	Control vs DHA Control vs DHA+ARA HM vs DHA HM vs DHA+ARA Control vs HM DHA vs DHA+ARA	0.612 0.416 0.000 0.013 0.001 0.199
		DHA	32	8.791	0.250	9.132			
		DHA+ARA	38	8.576	0.188	8.472			
		HM	56	7.727	0.203	7.618			
48 Weeks PCA	24:1	Control	37	0.067	0.016	0.035	0.943		
		DHA	32	0.049	0.009	0.034			
		DHA+ARA	38	0.046	0.008	0.036			
		HM	56	0.062	0.016	0.027			

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Table 10

## Red Blood Cell Phosphatidylethanolamine Fatty Acids

Time	Fatty Acid	Regimen	n	Arithmetic Mean	Standard Error	Median	Regimen p-value	Pairwise Comparison	Pairwise p-value
48 Weeks PCA	22:5n6	Control	37	1.401	0.066	1.411	0.000	Control vs DHA	0.977
		DHA	32	1.353	0.057	1.414		Control vs DHA+ARA	0.997
		DHA+ARA	38	1.364	0.054	1.359		HM vs DHA	0.000
		HM	56	1.883	0.056	1.889		HM vs DHA+ARA	0.000
48 Weeks PCA	22:4n3	Control	37	0.000	0.000	0.000	1.000	Control vs HM	0.000
		DHA	32	0.000	0.000	0.000		DHA vs DHA+ARA	0.975
		DHA+ARA	38	0.000	0.000	0.000			
		HM	56	0.001	0.001	0.000			
48 Weeks PCA	22:5n3	Control	37	2.567	0.092	2.681	0.000	Control vs DHA	0.884
		DHA	32	2.561	0.086	2.630		Control vs DHA+ARA	0.148
		DHA+ARA	38	2.436	0.066	2.443		HM vs DHA	0.000
		HM	56	1.942	0.065	1.978		HM vs DHA+ARA	0.000
48 Weeks PCA	22:6n3	Control	37	3.196	0.159	3.013	0.000	Control vs HM	0.213
		DHA	32	4.143	0.177	4.079		Control vs DHA+ARA	0.000
		DHA+ARA	38	3.801	0.134	3.721		HM vs DHA	0.000
		HM	56	7.283	0.201	7.341		HM vs DHA+ARA	0.000
								Control vs HM	0.000
								DHA vs DHA+ARA	0.281

Table 11  
Preterm Infant Complications

	Regimen			p-value*
	Control	DHA	DHA+ARA	
Retinopathy of Prematurity Test Results				
Absent	34 (76%)	44 (76%)	41 (79%)	0.91
I	8 (18%)	11 (19%)	6 (12%)	
II	2 (4%)	2 (3%)	4 (8%)	
III	1 (2%)	1 (2%)		
Present, but not graded			1 (2%)	
Ultrasound Examination for Intraventricular Hemorrhage				
None	47 (81%)	52 (84%)	49 (80%)	0.78
Stage 1	6 (10%)	9 (15%)	7 (11%)	
Stage 2	3 (5%)		2 (3%)	
Stage 3	1 (2%)		1 (2%)	
Stage 4	1 (2%)		2 (3%)	
Questionable		1 (2%)		
Posthemorrhagic Hydrocephalus developed?				
No	61 (98%)	65 (98%)	64 (97%)	1.00
Yes	1 (2%)	1 (2%)	2 (3%)	

\*The statistical test was based on a dichotomous response: present or absent.

Table 12

## Serious Adverse Events Reported During Study Formula Phase

Event	Regimen			p-value
	Control	DHA	DHA+ARA	
Any Event	4 (6%)	3 (5%)	4 (6%)	0.93
Other Respiratory Conditions of Fetus and Newborn	2 (3%)	0	0	0.10
Other Infection Specific to the Perinatal Period	1 (2%)	0	0	0.32
Intraventricular Hemorrhage	0	0	1 (2%)	1.00
Other Specified Perinatal Disorders of Digestive System	0	1 (2%)	0	1.00
Convulsions in Newborn	1 (2%)	0	0	0.32
Feeding Problems in Newborn	0	1 (2%)	1 (2%)	1.00
Hernia	0	0	1 (2%)	1.00
Other	0	1 (2%)	1 (2%)	1.00

Table 13

## Serious Adverse Events Reported During the Term Formula Phase

Event	Regimen				p-value
	Control	DHA	DHA + ARA	HM	
Any Event	7 (13%)	9 (15%)	9 (15%)	1 (1%)	0.002 C vs D 0.79 C vs D+A 0.79 D vs D+A 1.00 C vs HM 0.006 D vs HM 0.001 D+A vs HM 0.001
Infectious Colitis, Enteritis, and Gastroenteritis	0	0	1 (2%)	0	0.67
Croup	0	0	1 (2%)	0	0.67
Bronchopneumonia, Organism Unspecified	2 (4%)	3 (5%)	6 (10%)	0	0.013 C vs D 1.00 C vs D+A 0.27 D vs D+A 0.49 C vs HM 0.15 D vs HM 0.064 D+A vs HM 0.004
Asthma, Unspecified	1 (2%)	0	0	0	0.21
Esophageal Reflux	0	1 (2%)	2 (3%)	0	0.23
Dyspepsia and Other Stomach Function Disorder	0	0	0	1 (1%)	1.0
Other Respiratory Conditions of Fetus and Newborn	1 (2%)	1 (2%)	3 (5%)	0	0.11
Convulsions	1 (2%)	0	0	0	0.21
Sudden Infant Death Syndrome	1 (2%)	1 (2%)	0	0	0.34
Hernia	2 (4%)	2 (3%)	0	0	0.11
Other	0	3 (5%)	2 (3%)	0	0.063

Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9698-0301	Weight (g) Age (weeks pca)	1120 30.3	1240 31.3	1360 32.1	1590 33.1	1870 34.1					27.7			
Male	Control	9698-0304	Weight (g) Age (weeks pca)	1450 32.6	1630 33.4	1940 34.7	2180 35.4						36.1	3731 40.3	5752 48.3	6816 56.6
Male	Control	9699-0302	Weight (g) Age (weeks pca)	958.0 30.7	1108 31.7	1251 32.7	1378 33.7	1659 34.7					23.9	3064 39.9	4993 48.0	6553 57.9
Male	Control	9699-0306	Weight (g) Age (weeks pca)	1185 31.0	1261 32.0	1437 33.0	1647 34.0	1933 35.0					26.9	3575 40.3	4936 48.3	6014 57.1
Male	Control	9699-0308	Weight (g) Age (weeks pca)	1600 34.4	1840 35.4	2752 38.3							43.3	3688 40.3	5504 48.3	6922 57.3
Male	Control	9700-0301	Weight (g) Age (weeks pca)	1810 32.1	1855 32.6	2075 33.4	2330 34.4	2595 35.4	3120 37.4				36.2	3745 40.1	5080 47.6	6610 56.7
Male	Control	9701-0303	Weight (g) Age (weeks pca)	1181 32.4	1298 33.4	1494 34.4	1785 35.4	2012 36.3					31.5	3070 41.6	3895 48.6	4965 57.6
Male	Control	9701-0304	Weight (g) Age (weeks pca)	1412 31.9	1566 32.9	1851 33.7	2117 34.7	2318 35.9					34.1	3070 39.9	5445 48.3	7135 56.9
Male	Control	9702-0302	Weight (g) Age (weeks pca)	1480 31.0	1775 32.1	2045 33.0	2240 34.0	2340 34.6	2570 35.6				33.8	3590 40.1	4840 48.6	6110 58.4
Male	Control	9703-0302	Weight (g) Age (weeks pca)	1785 33.3	2040 34.6	2375 35.6	2685 36.4	2955 37.4					41.7	3620 39.7	5850 48.6	7470 57.3
Male	Control	9703-0304	Weight (g) Age (weeks pca)	1475 31.7	1705 33.0	1920 34.0	2190 34.9	2425 35.7					34.2	3170 40.1	5240 47.7	6970 57.1
Male	Control	9703-0308	Weight (g) Age (weeks pca)	1140 31.7	1230 32.6	1445 33.7	1665 34.7	1945 35.7					28.9	2520 39.7	4010 48.4	5030 56.9
Male	Control	9704-0303	Weight (g) Age (weeks pca)	975.0 32.3	1205 33.4	1270 34.4	1450 35.4	1665 36.3	1760 37.3	2045 38.3			24.4	2150 39.3	3700 48.3	4950 57.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.



Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9704-0305	Weight (g) Age (weeks pca)	1315 30.9	1475 32.0	1640 33.0	1860 34.1						23.7			
Male	Control	9705-0302	Weight (g) Age (weeks pca)	1280 33.0	1389 34.0	1588 35.0	1786 36.0	2240 37.4					30.9	2540 39.6	4936 47.4	5646 56.4
Male	Control	9705-0304	Weight (g) Age (weeks pca)	1270 31.3	1280 32.3	1570 33.3	1810 34.6						25.3	3291 39.7	5816 47.7	7490 56.7
Male	Control	9706-0302	Weight (g) Age (weeks pca)	1645 35.7	1865 36.6	2130 37.7	2435 38.7						37.1	2800 40.1	4660 48.7	6170 56.7
Male	Control	9706-0303	Weight (g) Age (weeks pca)	1875 33.7	1984 34.7	2135 35.6	2185 36.4	2465 37.3					22.2	3050 41.0	4550 48.6	6675 56.9
Male	Control	9706-0308	Weight (g) Age (weeks pca)	1655 32.9	1734 33.1	2005 34.0	2495 35.4						46.9	3835 40.6	5155 48.0	6090 56.3
Male	Control	9707-0302	Weight (g) Age (weeks pca)	1544 31.6	1820 32.9	2215 34.4	2450 35.4	2460 35.7					32.8	2930 40.1	3795 47.7	5185 56.6
Male	Control	9707-0303	Weight (g) Age (weeks pca)	1415 33.1	1600 34.1	1850 35.1	2195 36.6	2310 37.1					32.7	2530 39.7	4235 47.7	6530 57.1
Male	Control	9707-0309	Weight (g) Age (weeks pca)	1046 30.9	1442 32.7	1644 33.7	1910 34.9						30.7	2965 39.9	4465 48.0	
Male	Control	9708-0303	Weight (g) Age (weeks pca)	1730 32.7	1960 33.7	2205 34.7	2520 35.7						37.4	3680 40.1	5470 48.1	7330 57.0
Male	Control	9709-0302	Weight (g) Age (weeks pca)	1090 29.9	1440 31.7	1660 32.7	1910 33.7	2040 34.3					30.8	3845 39.9	5700 48.0	6775 56.7
Male	Control	9712-0301*	Weight (g) Age (weeks pca)	1245 31.6	1221 31.7	1245 31.9	1291 32.0	1294 32.1	1330 32.3	1369 32.4	1402 32.6	1433 32.7	26.1			
Male	Control	9712-0302	Weight (g) Age (weeks pca)	1292 33.1	1345 34.1	1456 35.1	1670 36.1	1835 37.1	1985 38.1				21.0	2160 40.1	3300 47.7	3980 57.3

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	Control	9743-0301	Weight (g) Age (weeks pca)	1520 34.1	1570 35.0	1670 36.0	1720 37.1						10.0	2260 41.0	4535 50.0	
Male	Control	9746-0301	Weight (g) Age (weeks pca)	2065 37.6	2465 38.9	2760 39.7	3085 40.6	3085 40.6					48.9	3085 40.6	4795 47.6	6695 57.6
Male	DIHA	9698-0302	Weight (g) Age (weeks pca)	1640 35.1	1860 36.1	3170 39.9							47.5	3170 39.9	5206 47.9	7036 57.1
Male	DIHA	9698-0306	Weight (g) Age (weeks pca)	1620 35.1	1830 36.3	2090 37.3	2575 40.0						28.3	2575 40.0	4334 48.0	6022 57.0
Male	DIHA	9699-0301	Weight (g) Age (weeks pca)	1018 31.3	1207 32.3	1360 33.3	1617 34.3						27.9	3121 39.9	5192 48.0	6752 57.9
Male	DIHA	9699-0303	Weight (g) Age (weeks pca)	1258 32.4	1435 33.4	1631 34.4	1882 35.4	2724 36.4					48.3	2724 40.1	4341 48.1	5674 57.0
Male	DIHA	9699-0307	Weight (g) Age (weeks pca)	1182 34.7	1358 35.7	1484 36.7	1666 37.7						22.5	1986 40.0	3206 48.0	4511 57.0
Male	DIHA	9700-0303	Weight (g) Age (weeks pca)	1830 33.9	1980 34.4	2450 35.9	3045 37.7						45.4	3585 39.6	5420 47.4	7035 56.7
Male	DIHA	9701-0301	Weight (g) Age (weeks pca)	1098 29.6	1234 30.6	1365 31.6	1689 33.4	1902 34.6	2019 35.6	2104 36.4	2276 37.4	2288 38.6	20.4	2805 40.4	3405 47.6	4660 57.0
Male	DIHA	9701-0305	Weight (g) Age (weeks pca)	1621 31.7	1829 33.1	1880 33.7	2253 34.7	2582 35.7					34.7	3660 39.7		
Male	DIHA	9703-0303	Weight (g) Age (weeks pca)	1775 33.3	2030 34.1	2285 35.1	2595 36.0	2780 37.1					38.2	3080 39.9	3940 48.0	5260 56.9
Male	DIHA	9703-0306	Weight (g) Age (weeks pca)	1725 33.4	1870 34.0	2180 35.0							41.7			
Male	DIHA	9703-0307	Weight (g) Age (weeks pca)	1525 32.7	1725 33.7	2020 34.9	2390 36.0						37.6	3120 40.7	4410 47.9	5600 56.9

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DHA	9704-0304	Weight (g) Age (weeks pca)	1380 32.1	1570 33.1	1730 34.1	1960 35.0	2140 35.9					29.3	2880 40.3	3900 48.3	4300 57.3
Male	DHA	9704-0306	Weight (g) Age (weeks pca)	1320 30.7	1370 31.7	1550 32.7	1760 33.7	2020 34.7	2170 35.9				25.6		3750 48.0	4800 57.0
Male	DHA	9705-0303	Weight (g) Age (weeks pca)	1380 33.0	1446 34.0	1616 35.0	1843 36.0	2330 37.4					30.8	2370 39.6	4170 47.4	5787 56.4
Male	DHA	9705-0305	Weight (g) Age (weeks pca)	1490 31.1	1770 32.1	1980 33.1	2240 34.0						36.7	3291 39.6		
Male	DHA	9706-0304	Weight (g) Age (weeks pca)	1490 33.0	1655 33.7	1915 34.7	2260 36.0						36.8	3335 40.0	5265 48.1	6900 57.3
Male	DHA	9706-0306	Weight (g) Age (weeks pca)	1604 34.4	1908 35.4	2160 36.3							42.8	3310 41.4	4205 47.6	5600 56.9
Male	DHA	9707-0001	Weight (g) Age (weeks pca)	1305 31.0	1429 32.0								17.7			
Male	DHA	9707-0304	Weight (g) Age (weeks pca)	1555 32.0	1740 33.0	1990 34.0	2400 35.4	2570 36.0					36.9	3280 39.9	5115 48.0	6755 57.6
Male	DHA	9707-0306	Weight (g) Age (weeks pca)	1728 36.1	2040 37.3	2260 38.1	3050 40.6	3050 40.6					43.2	3050 40.6	5100 48.6	7150 57.6
Male	DHA	9707-0307*	Weight (g) Age (weeks pca)	1649 32.4	1675 32.6	1699 32.7	1732 32.9	1778 33.0	1811 33.1	1858 33.3	1882 33.4	1938 33.6	39.6			
Male	DHA	9707-1308	Weight (g) Age (weeks pca)	1780 34.4	2045 35.7	3004 39.3	3004 39.3						36.7	3004 39.3	4420 47.3	6090 57.7
Male	DHA	9707-2308	Weight (g) Age (weeks pca)	1651 34.4	1923 35.7	2850 39.3	2850 39.3						35.8	2850 39.3	4375 47.3	5930 57.7
Male	DHA	9708-0302	Weight (g) Age (weeks pca)	1485 33.3	1740 34.3	2500 37.0							39.2	3873 42.9		6256 57.3

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DIIA	9709-0301	Weight (g) Age (weeks pca)	1490 32.4	1740 33.4	2000 34.4	2400 35.4	2800 36.7					44.4	3150 39.4	5080 47.4	6750 56.4
Male	DIIA	9709-0304	Weight (g) Age (weeks pca)	1470 34.4	1520 35.4								7.1			
Male	DIIA	9712-0304	Weight (g) Age (weeks pca)	1545 33.0	1800 34.0	1985 35.0	2160 36.0	2550 37.6					30.5	3160 40.3	5200 48.1	7300 57.1
Male	DIIA	9712-0306	Weight (g) Age (weeks pca)	1240 31.5	1435 32.5	1695 33.5	1945 34.5						33.9	3040 39.6	4680 48.6	5860 57.6
Male	DIIA	9743-0303	Weight (g) Age (weeks pca)	1700 32.9	1810 33.9	2100 34.9	2300 35.7						31.1	3100 40.6	5500 48.6	
Male	DIIA	9743-0304	Weight (g) Age (weeks pca)	1530 32.3	1880 34.0	2160 35.0	2375 36.0	2440 36.4					32.2	3628 38.1	5840 50.6	
Male	DIIA+ARA	9698-0305	Weight (g) Age (weeks pca)	1120 30.7	1340 32.6	1550 33.6							20.9	2440 37.4	5525 47.6	6646 56.6
Male	DIIA+ARA	9698-0308	Weight (g) Age (weeks pca)	1410 31.1	1690 32.4	1870 33.3	2120 34.3						32.0	3553 40.3	6007 47.6	7937 57.3
Male	DIIA+ARA	9699-0304	Weight (g) Age (weeks pca)	1499 36.1	1689 37.1	1950 38.1	2355 40.3						29.8	2355 40.3	3404 48.0	4993 57.1
Male	DIIA+ARA	9699-0305	Weight (g) Age (weeks pca)	1056 32.0	1134 33.0	1290 34.0	1490 35.7						17.2	2610 40.6	4256 48.7	5050 57.6
Male	DIIA+ARA	9700-0302	Weight (g) Age (weeks pca)	1635 33.9	1880 34.7	2235 35.9	2570 36.9	2735 37.9					40.7	3255 39.7	5540 47.7	7380 56.7
Male	DIIA+ARA	9701-0302	Weight (g) Age (weeks pca)	1442 33.6	1686 34.6	2045 35.6	2835 37.7						48.9	3240 39.7	5055 46.7	6600 56.7
Male	DIIA+ARA	9701-0306	Weight (g) Age (weeks pca)	1587 32.3	2037 33.4	2245 34.4	2460 35.3	2756 36.3	3072 37.3	3228 37.7			41.4	3960 42.3	5200 48.4	

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DHA+ARA	9701-0307	Weight (g) Age (weeks pca)	1397 33.3	1710 34.3	1919 35.1	2932 38.4						42.5	3445 40.6	5930 48.6	7475 57.4
Male	DHA+ARA	9702-0301	Weight (g) Age (weeks pca)	1670 32.0	1865 33.0	2160 34.0	2660 36.0						36.0	3780 40.6	5250 47.6	
Male	DHA+ARA	9702-0303	Weight (g) Age (weeks pca)	1650 32.9	1905 33.9	2660 36.4							40.7	3500 40.0	5160 48.0	6520 56.4
Male	DHA+ARA	9703-0301	Weight (g) Age (weeks pca)	1255 29.4	1460 30.4	1745 31.3	2055 32.3	2415 33.4					42.3	4350 40.4	6020 47.4	6720 56.6
Male	DHA+ARA	9703-0305	Weight (g) Age (weeks pca)	1440 32.0	1635 33.0	1830 34.0	2115 35.0	2390 36.1	2590 36.9				34.1	3170 40.0	4330 47.9	5630 56.7
Male	DHA+ARA	9704-0301	Weight (g) Age (weeks pca)	1110 30.6	1270 31.6	1490 32.4	1740 33.4	2050 34.4					35.1	3220 39.9	5460 47.7	7050 56.7
Male	DHA+ARA	9704-0302	Weight (g) Age (weeks pca)	1080 32.0	1230 33.0	1370 34.0	1520 34.9	1680 36.0	1840 36.9				22.2	2570 40.0	6540 48.1	8050 57.4
Male	DHA+ARA	9705-0301	Weight (g) Age (weeks pca)	1300 32.7	1440 33.7	1620 34.7	1870 35.7						27.0	2979 40.1	4400 48.1	5873 58.0
Male	DHA+ARA	9705-0306	Weight (g) Age (weeks pca)	1320 31.4	1490 32.4	1700 33.4	2020 34.4	2300 35.9					32.7	3631 39.9	5447 47.9	6809 56.9
Male	DHA+ARA	9705-0307	Weight (g) Age (weeks pca)	1480 34.4	1650 35.4	1810 36.1	2240 37.4						36.4	3007 39.9	5589 48.4	6596 56.7
Male	DHA+ARA	9706-0305	Weight (g) Age (weeks pca)	1330 33.9	1455 34.4	1660 35.4	1930 36.6						31.4	2695 39.9	4820 48.1	6225 58.1
Male	DHA+ARA	9706-0307	Weight (g) Age (weeks pca)	1355 31.9	1585 33.0	1825 33.9	2270 35.1						40.0	3585 40.4	5955 49.1	6925 57.6
Male	DHA+ARA	9706-0309	Weight (g) Age (weeks pca)	1620 34.1	1910 35.3	2150 36.0							40.3	3460 40.9	5255 48.7	5775 57.4

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	DIHA+ARA	9707-0301	Weight (g) Age (weeks pca)	1553 32.6	1980 34.3	2280 35.3	2720 36.6						41.5	3395 40.1	4950 47.9	6285 56.9
Male	DIHA+ARA	9707-0305	Weight (g) Age (weeks pca)	1755 33.9	1990 34.7	2245 35.7	2505 36.7	2770 37.7					37.4			
Male	DIHA+ARA	9707-0310	Weight (g) Age (weeks pca)	1620 32.7	1828 33.7	2140 34.7	3195 37.9						44.8	3585 39.7	5170 47.9	6725 56.3
Male	DIHA+ARA	9708-0301	Weight (g) Age (weeks pca)	1640 32.7	1880 33.7	2200 34.7	2420 35.7						38.0	3730 40.1	4835 47.9	6185 57.0
Male	DIHA+ARA	9708-0304	Weight (g) Age (weeks pca)	1680 34.6	2180 35.9								55.6			
Male	DIHA+ARA	9709-0303	Weight (g) Age (weeks pca)	1470 32.6	1810 33.6								48.6			
Male	DIHA+ARA	9709-0305	Weight (g) Age (weeks pca)	1410 34.4	1655 35.4	1900 36.4	2160 37.4						35.6	2630 39.7	4570 47.7	5520 57.1
Male	DIHA+ARA	9712-0303	Weight (g) Age (weeks pca)	1180 31.4	1210 32.3	1450 33.4	1590 34.4						20.9	2520 40.4	3500 47.4	5010 56.4
Male	DIHA+ARA	9712-0305	Weight (g) Age (weeks pca)	1325 31.5	1505 32.5	1785 33.5	2010 34.5	2300 35.6					34.1	3030 39.6	4350 48.6	5510 57.6
Male	DIHA+ARA	9723-0301	Weight (g) Age (weeks pca)	1630 33.9	1728 34.9	1961 35.9	2214 36.9						28.4	3104 40.3		5986 58.9
Male	HH	9698-0601												3518 40.0	5497 48.3	6582 56.9
Male	HH	9698-0602												3177 40.0	5220 48.1	6355 57.0
Male	HH	9698-0603												3858 40.0	5447 48.0	6454 57.0

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IIM	9698-0604												4355 40.0	5092 48.0	6383 57.0
Male	IIM	9698-0605												3433 40.0	4979 48.1	6426 57.1
Male	IIM	9699-0501												3915 40.0	6639 48.3	7773 57.4
Male	IIM	9699-0502												3802 40.0	5787 48.4	7178 57.4
Male	IIM	9701-0601												3317 40.0	5555 47.9	7070 56.4
Male	IIM	9701-0602												3487 40.0	5833 47.3	8070 58.3
Male	IIM	9701-0603												3232 40.0	4940 47.4	5855 56.4
Male	IIM	9701-0604												3600 40.0	5215 47.9	6285 56.9
Male	IIM	9701-0605												3402 40.0	5575 47.6	7210 57.6
Male	IIM	9701-0606												3090 40.0	4485 47.7	5445 56.7
Male	IIM	9702-0601												3480 40.0	5780 48.6	6530 56.6
Male	IIM	9702-0602												3165 40.0	5060 48.3	6660 57.1
Male	IIM	9703-0502												2670 40.0	5420 48.3	7220 57.1

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IIM	9703-0503												4100 40.0	6740 47.4	8330 56.4
Male	IIM	9703-0504												3435 40.0	6000 48.1	7930 57.1
Male	IIM	9704-0502												3285 40.0	5220 48.1	6560 56.6
Male	IIM	9704-0503												3400 40.0	5200 48.7	6725 56.9
Male	IIM	9705-0601												3200 40.0	5617 48.3	6752 57.3
Male	IIM	9705-0602												3860 40.0	6227 48.0	
Male	IIM	9706-0601												3152 40.0	5105 49.0	6545 57.0
Male	IIM	9706-0602												3557 40.0	5175 47.4	7315 57.7
Male	IIM	9706-0603												3192 40.0	5070 47.9	6970 56.7
Male	IIM	9706-0604												3461 40.0	4225 48.0	5525 57.1
Male	IIM	9706-0605												3870 40.0	6220 48.1	7660 56.4
Male	IIM	9706-0606												4315 40.0	5975 48.3	6720 56.6
Male	IIM	9707-0601												3263 40.0	4730 48.1	5825 57.0

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	IIM	9707-0602												3206 40.0	4515 48.1	6220 57.7
Male	IIM	9707-0603												4256 40.0	6930 48.0	8810 57.0
Male	IIM	9707-0604												3419 40.0	5460 48.0	6130 56.7
Male	IIM	9707-0605												3433 40.0		
Male	IIM	9707-0606												3603 40.0	5825 48.4	
Male	IIM	9707-0607												3569 40.0	5410 47.9	6870 56.9
Male	IIM	9707-0608												3348 40.0	5135 48.0	6370 57.0
Male	IIM	9707-0609												3348 40.0		
Male	IIM	9708-0601												3064 40.0	5220 47.6	6595 56.4
Male	IIM	9708-0602												4085 40.0		
Male	IIM	9708-0603												3319 40.0	5135 48.4	6327 57.1
Male	IIM	9708-0604												3291 40.0		
Male	IIM	9708-0605												3796 40.0		

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Male	HM	9708-0606												4020 40.0	4645 48.4	5405 57.1
Male	IIM	9708-0607												3333 40.0	4043 47.9	5180 56.7
Male	IIM	9709-0505												3400 40.0		
Female	Control	9698-0003*	Weight (g) Age (weeks pca)	1020 31.1	1050 31.3	1070 31.4	1080 31.6	1080 31.7	1060 31.9	1080 32.0	1070 32.1		5.6			
Female	Control	9699-0001	Weight (g) Age (weeks pca)	1464 32.7	1672 33.7	1862 34.7	2000 35.7	2145 36.7					24.1	2610 39.7	4369 47.9	5220 56.9
Female	Control	9699-0003	Weight (g) Age (weeks pca)	1473 34.0	1629 35.0	1860 36.0	2497 38.0						37.3	2780 40.0	4596 48.0	5816 57.0
Female	Control	9701-0003	Weight (g) Age (weeks pca)	1480 34.6	1633 35.6	1903 36.6	1975 37.3	2292 38.6					29.1	2675 40.6	4165 48.6	5200 55.6
Female	Control	9701-0005	Weight (g) Age (weeks pca)	1174 30.7	1366 31.7	1555 32.7	1745 33.7	1976 34.7					28.3	3175 39.7	5140 48.4	6280 56.4
Female	Control	9701-0008	Weight (g) Age (weeks pca)	1391 34.3	1569 35.3	1898 36.4	2198 37.3	2406 37.9					41.1	2980 40.4	4425 47.4	5815 56.4
Female	Control	9701-0011	Weight (g) Age (weeks pca)	1050 30.6	1254 31.4	1492 32.4	1756 33.4	2044 34.4					36.6	2870 39.7	4420 48.6	5505 57.4
Female	Control	9702-0002	Weight (g) Age (weeks pca)	1222 31.7	1371 32.7	1570 34.1	1750 35.1	1995 36.0	2390 37.1				29.4	3380 40.4	4900 47.6	
Female	Control	9702-0004	Weight (g) Age (weeks pca)	1454 31.0	1555 31.9	1840 33.1	2530 36.0						31.6	3600 39.9	5160 47.7	6900 56.7
Female	Control	9702-0010	Weight (g) Age (weeks pca)	1775 34.0	2065 35.0	2410 36.0	2645 37.0						42.2	3060 39.9	4820 48.3	6690 57.6

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	Control	9703-0002	Weight (g) Age (weeks pca)	1170 29.1	1250 30.4	1390 31.3	1570 32.4	1825 33.4	2130 34.3				26.4	3210 39.6	4750 47.4	
Female	Control	9703-0005	Weight (g) Age (weeks pca)	1420 31.4	1590 32.3	1765 33.3	1900 33.9	2220 35.3					29.5	2610 37.3	4330 46.0	5640 55.0
Female	Control	9703-0008	Weight (g) Age (weeks pca)	1495 33.0	1715 34.0	2095 35.0	2445 36.0	2685 36.6					48.3	3360 40.1	4780 47.7	6410 56.1
Female	Control	9705-0004	Weight (g) Age (weeks pca)	1120 31.3	1290 32.3	1490 33.3	1660 34.0						28.3	2722 39.7	4085 46.6	5646 55.0
Female	Control	9706-0003	Weight (g) Age (weeks pca)	1515 35.1	1673 36.3	1965 37.1	2330 38.3					37.9				
Female	Control	9706-0005	Weight (g) Age (weeks pca)	1485 33.0	1610 33.7	1805 34.7	2150 36.0						31.7	2740 40.0	4165 48.1	5305 57.3
Female	Control	9706-0009	Weight (g) Age (weeks pca)	1525 32.3	1620 32.9	1960 34.3							31.6	3640 40.3	5495 47.6	7225 53.4
Female	Control	9706-0010	Weight (g) Age (weeks pca)	1905 34.3	2185 35.0								56.0	3655 40.0	5390 48.4	6535 56.7
Female	Control	9706-0013	Weight (g) Age (weeks pca)	1185 31.6	1270 32.4	1585 33.6	1810 34.6						31.1	2680 40.1	3800 48.4	
Female	Control	9706-0016	Weight (g) Age (weeks pca)	1510 32.0	1765 33.1	1935 33.9							32.6	3320 40.7	4535 48.7	5297 56.6
Female	Control	9707-0003	Weight (g) Age (weeks pca)	1465 32.0	1505 32.6	1655 33.6	2010 35.3	2325 36.4	2765 38.3				30.2	3110 40.1	4125 48.1	4995 57.1
Female	Control	9707-0006	Weight (g) Age (weeks pca)	1866 34.6	3430 40.0	3430 40.0							41.2	3430 40.0	5385 48.9	7250 57.3
Female	Control	9707-1006	Weight (g) Age (weeks pca)	1815 34.6	3330 40.0	3330 40.0							39.9	3330 40.0	5490 48.9	6920 57.3

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	Control	9708-0001	Weight (g) Age (weeks pca)	1410 33.4	1600 34.4	1850 35.4	2050 36.9						27.2	2910 40.6	4734 48.4	
Female	Control	9708-0003	Weight (g) Age (weeks pca)	940.0 30.0	970.0 31.0								4.3			
Female	Control	9708-0008	Weight (g) Age (weeks pca)	1380 32.9	1605 33.7	1860 34.9	2180 36.3						33.1	2582 39.3	4110 47.4	5361 57.1
Female	Control	9709-0002	Weight (g) Age (weeks pca)	1980 32.7	2225 33.7	2400 34.7							30.0			
Female	Control	9709-0005	Weight (g) Age (weeks pca)	1175 31.9	1425 33.3	1665 34.6	1945 35.6	2200 36.3					32.3	2975 39.6	4700 48.4	5900 56.7
Female	Control	9712-0005	Weight (g) Age (weeks pca)	972.0 29.1	1145 30.1	1290 31.1	1490 32.1	1695 33.1					25.6	2930 40.3	4450 47.6	5880 57.1
Female	Control	9712-0006	Weight (g) Age (weeks pca)	1203 31.9	1358 32.9	1585 33.9	1790 34.9						28.4	3030 39.7	4560 48.0	6230 57.0
Female	Control	9743-0003	Weight (g) Age (weeks pca)	1300 31.6	1520 33.4	1740 34.1	1890 35.1						24.0		4000 48.4	5160 57.4
Female	Control	9746-0001	Weight (g) Age (weeks pca)	1420 32.6	1740 33.6	2075 34.6	2320 35.6	2625 36.6					42.7	3170 39.7	4145 47.6	5192 56.6
Female	DIHA	9698-0004	Weight (g) Age (weeks pca)	1410 30.1	1650 31.1	1890 32.1	2140 33.1						34.7	3787 40.0	4795 48.0	6291 57.0
Female	DIHA	9698-0006	Weight (g) Age (weeks pca)	1110 30.7	1240 31.7	1420 32.7	1720 33.7						28.7			
Female	DIHA	9698-0009	Weight (g) Age (weeks pca)	1205 30.3	1310 31.4	1520 32.4	1630 33.1	2020 34.9					25.9	2891 40.0	3979 48.0	5121 57.0
Female	DIHA	9698-0307	Weight (g) Age (weeks pca)	1790 34.4	2110 35.7	2450 37.6							29.7	3135 39.4	5185 47.4	6695 56.4

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DIHA	9699-0002	Weight (g) Age (weeks pca)	1313 32.9	1477 33.9	1669 34.9	1929 35.9	2380 36.9					36.9	3177 39.7	5787 47.7	7093 56.7
Female	DIHA	9700-0001	Weight (g) Age (weeks pca)	1580 32.4	1820 33.4	2050 34.3	2295 35.3	2500 36.3					34.5	3210 40.1	5110 48.1	6300 57.1
Female	DIHA	9701-0001	Weight (g) Age (weeks pca)	1300 33.0	1356 34.0	1586 35.0	1924 36.0	2125 36.6					34.2	2910 39.6	4325 48.0	5625 57.0
Female	DHA	9701-0004	Weight (g) Age (weeks pca)	1108 30.7	1261 31.7	1441 32.7	1671 33.7	1897 34.7					28.4	3020 39.7	4855 48.4	6040 56.4
Female	DHA	9701-0012	Weight (g) Age (weeks pca)	1674 34.9	1928 35.9	2151 36.9	2311 37.6	2685 39.6	2685 39.6				30.1	2685 39.6		
Female	DIHA	9701-0014	Weight (g) Age (weeks pca)	1422 33.9	1631 34.9	1858 35.9	2455 37.9						37.2	2970 39.9	4605 47.7	5140 56.9
Female	DIHA	9702-0001	Weight (g) Age (weeks pca)	1780 31.6	2115 32.9	2390 33.9	3000 36.4						35.8	3850 40.0	5610 49.6	6600 57.0
Female	DIHA	9702-0006	Weight (g) Age (weeks pca)	1850 35.4	2005 36.1	2650 39.6	2650 39.6						27.3	2650 39.6	4450 48.4	6020 56.4
Female	DIHA	9702-0007	Weight (g) Age (weeks pca)	1285 31.1	1459 32.1	1780 33.6	1965 34.4	2035 34.9					29.6			
Female	DIHA	9702-0008	Weight (g) Age (weeks pca)	1605 34.1	1930 35.1	3540 39.6	3540 39.6						51.3	3540 39.6	5920 47.6	7820 57.1
Female	DIHA	9703-0003	Weight (g) Age (weeks pca)	1255 34.4	1355 35.1	1535 36.1	1845 37.1	2150 38.1					34.8	2430 39.4	4130 48.0	5010 56.1
Female	DIHA	9703-0004	Weight (g) Age (weeks pca)	1170 32.6	1340 33.3	1550 34.3	1795 35.3	2225 37.0					33.9	2870 39.4	4610 48.1	6490 57.1
Female	DHA	9703-0009	Weight (g) Age (weeks pca)	1570 33.3	1830 34.3	2095 35.1	2395 36.3	2655 37.9					34.6	3160 40.4	4480 48.4	5570 58.0

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA	9704-0004	Weight (g) Age (weeks pca)	1440 33.6	1670 34.6	1740 35.0							30.5	3100 40.0	5830 48.0	8630 57.0
Female	DHA	9704-0005	Weight (g) Age (weeks pca)	1050 29.7	1310 30.9	1490 31.7	1700 32.7	1890 33.7					30.0	3360 39.6	4860 48.0	6100 57.0
Female	DHA	9705-0001	Weight (g) Age (weeks pca)	1220 32.7	1370 33.6	1590 34.7	1880 35.7	2098 36.7					31.9	3092 40.1	4795 48.1	5986 57.1
Female	DHA	9706-0006	Weight (g) Age (weeks pca)	1270 33.0	1405 33.7	1630 34.7	1930 36.0						31.7	2705 40.0	4145 48.1	5320 57.3
Female	DHA	9706-0008	Weight (g) Age (weeks pca)	990.0 33.4	1188 34.6	1345 35.7	1485 36.4						23.0	2120 39.9		
Female	DHA	9706-0012	Weight (g) Age (weeks pca)	1610 31.6	1830 32.4	2130 33.6	2280 34.6						32.5	3530 40.1	4790 48.4	
Female	DHA	9706-0014	Weight (g) Age (weeks pca)	1080 31.3	1170 32.6	1395 33.4	1560 34.4	1804 35.3					26.2	3295 40.6	5600 49.4	7675 58.0
Female	DHA	9707-0004	Weight (g) Age (weeks pca)	1635 34.0	1771 35.0	2850 38.7							38.1	3045 40.0	4595 48.0	5765 57.0
Female	DHA	9707-0308	Weight (g) Age (weeks pca)	2005 34.4	3440 39.3	3440 39.3							42.2	3440 39.3	4800 47.3	6360 57.7
Female	DHA	9708-0004	Weight (g) Age (weeks pca)	1460 32.6	1665 33.6	1955 34.6	2280 35.6	2485 36.6					38.1			
Female	DHA	9708-0006	Weight (g) Age (weeks pca)	1485 33.7	1775 34.7	2110 35.7	2380 37.0						39.5	3010 40.1	4620 48.1	6530 57.0
Female	DHA	9709-0001	Weight (g) Age (weeks pca)	1250 29.6	1490 31.0	1755 32.0	1970 33.0	2250 34.0	2520 35.0				33.8	3500 40.1		
Female	DHA	9709-0003	Weight (g) Age (weeks pca)	1540 34.4	1725 35.4	2015 36.4	2155 37.4						30.5	2580 40.3	4080 47.7	5420 57.1

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DIHA	9712-0001	Weight (g) Age (weeks pca)	987.0 30.0	1120 31.0	1270 32.0	1470 33.0	1685 34.0					24.9	2940 40.1	3980 48.1	5250 57.1
Female	DIHA	9712-0002	Weight (g) Age (weeks pca)	1060 32.7	1230 33.7	1430 34.7							26.4			
Female	DIHA	9712-0007	Weight (g) Age (weeks pca)	1082 32.7	1230 33.7	1440 34.7	1650 35.7						27.3	2425 39.7	4250 47.9	5340 56.9
Female	DIHA	9743-0001	Weight (g) Age (weeks pca)	1000 32.1	1170 33.1	1470 34.4	1800 35.7	1930 36.1					33.5		4140 48.3	5400 57.3
Female	DIHA	9743-0002	Weight (g) Age (weeks pca)	1380 32.1	1570 33.3	1845 34.1	1975 35.1						29.7		4540 48.4	5160 57.4
Female	DIHA+ARA	9698-0001	Weight (g) Age (weeks pca)	1550 31.6	1690 32.6	2000 33.6	2380 34.9						37.1	3530 40.0	5348 47.7	6582 56.7
Female	DIHA+ARA	9698-0002	Weight (g) Age (weeks pca)	1580 32.6	1870 33.7	2130 34.6	2260 35.7						31.8	3241 40.7		
Female	DIHA+ARA	9699-0004	Weight (g) Age (weeks pca)	985.0 31.0	1122 32.0	1283 33.0	1536 34.0	1788 35.0					28.9	3177 41.3	5107 48.3	6979 57.3
Female	DIHA+ARA	9699-0005	Weight (g) Age (weeks pca)	1330 31.9	1542 32.9	1688 33.9	2000 34.9	2330 35.9					35.1	4029 40.0	6752 48.0	8341 57.0
Female	DIHA+ARA	9700-0002	Weight (g) Age (weeks pca)	1315 30.3	1525 31.3	1885 32.3	2035 33.3	2220 34.1	2480 35.6				31.9	3340 40.3	4930 48.1	6420 57.1
Female	DIHA+ARA	9701-0002	Weight (g) Age (weeks pca)	1398 33.4	1609 34.4	1887 35.4	2210 36.4	2420 37.4					37.8	2930 39.4	5115 48.4	6525 56.4
Female	DIHA+ARA	9701-0006	Weight (g) Age (weeks pca)	1720 32.3	1859 33.3	2113 34.3	2456 35.3	2728 36.1					38.3	3600 40.3	5045 48.0	6270 57.3
Female	DIHA+ARA	9701-0007	Weight (g) Age (weeks pca)	1469 33.7	1427 34.9	1590 35.7	1982 36.7	2227 37.7					29.8	2680 39.9	4935 47.9	6955 56.9

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DIIA+ARA	9701-0010	Weight (g) Age (weeks pca)	1488 32.3	1703 33.4	1978 34.4	2234 35.3	2433 36.1	2759 37.7				34.6	3500 41.1	5545 48.4	
Female	DIIA+ARA	9701-0013	Weight (g) Age (weeks pca)	1841 33.0	2019 33.7								35.6		4545 48.7	5550 57.4
Female	DIIA+ARA	9702-0003	Weight (g) Age (weeks pca)	1293 30.1	1488 31.1	1820 32.1	2155 33.4	2400 34.1					39.9	4190 40.0	6220 48.4	7500 56.9
Female	DIIA+ARA	9702-0005	Weight (g) Age (weeks pca)	1895 34.0	2060 35.0	2300 36.0	2525 37.0	2710 38.0					29.9	3025 40.0	4300 47.4	5340 56.4
Female	DIIA+ARA	9702-0009	Weight (g) Age (weeks pca)	1725 34.0	2000 35.0	2230 36.0	2595 37.0	2655 37.3					40.9	2905 39.9	4680 48.3	6410 57.6
Female	DIIA+ARA	9703-0001	Weight (g) Age (weeks pca)	1145 31.3	1255 32.1	1450 33.1	1680 34.3	1955 35.3					28.9	3030 41.0	4250 48.1	5420 57.3
Female	DIIA+ARA	9703-0006	Weight (g) Age (weeks pca)	1865 34.0	2200 35.0	2560 35.9	2880 37.0						49.1	3600 40.0	5400 48.1	6650 56.7
Female	DIIA+ARA	9703-0007	Weight (g) Age (weeks pca)	1390 32.0	1495 33.1	1620 34.0	1880 35.0	2030 35.7	2240 36.6				27.4	2850 40.0	4190 47.9	5850 56.7
Female	DIIA+ARA	9704-0002	Weight (g) Age (weeks pca)	960.0 29.0	1090 30.0	1200 30.9	1370 31.9	1570 32.9	1780 33.9	2070 34.9			26.7	3110 40.0	5150 48.0	6800 57.3
Female	DIIA+ARA	9704-0003	Weight (g) Age (weeks pca)	1690 32.7	1840 33.4								30.0	4000 40.0	5400 48.0	6640 57.0
Female	DIIA+ARA	9705-0003	Weight (g) Age (weeks pca)	1760 34.4	2260 35.7	2500 36.6	2920 37.7						49.8	3376 39.9	5107 48.4	6894 56.9
Female	DIIA+ARA	9705-0005*	Weight (g) Age (weeks pca)	1075 31.1	1120 31.4	1185 31.7	1280 32.1	1310 32.4	1310 32.7	1265 33.0	1350 33.3	1380 33.4	22.1	2600 40.4	4000 48.0	5050 57.0
Female	DIIA+ARA	9706-0001	Weight (g) Age (weeks pca)	1290 31.7	1515 32.9	1685 33.7	2060 34.9						34.5	4100 40.1	6550 48.6	7655 56.7

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.



Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA+ARA	9706-0002	Weight (g) Age (weeks pca)	1395 31.9	1710 33.0	1884 33.9	2275 35.4						34.8	2845 40.3	4645 48.9	5550 57.3
Female	DHA+ARA	9706-0004	Weight (g) Age (weeks pca)	1550 36.7	1705 37.6	2050 38.7							36.1	2645 41.7	4225 49.7	4935 58.0
Female	DHA+ARA	9706-0007	Weight (g) Age (weeks pca)	1235 33.4	1490 34.6	1820 35.7	1930 36.4						34.3	2505 40.3		
Female	DHA+ARA	9706-0011	Weight (g) Age (weeks pca)	1900 34.3	2105 35.0								41.0	3430 40.0	5175 48.4	6140 56.7
Female	DHA+ARA	9706-0015	Weight (g) Age (weeks pca)	1670 34.6	1975 35.6	2210 36.4							41.6	3005 40.9	4465 48.4	5810 57.6
Female	DHA+ARA	9706-0017	Weight (g) Age (weeks pca)	1465 32.3	1700 33.4	1895 34.3	2170 35.3						33.4			
Female	DHA+ARA	9707-0002	Weight (g) Age (weeks pca)	1775 34.3	2240 36.0	2385 36.9	2610 37.9						33.2			
Female	DHA+ARA	9708-0002	Weight (g) Age (weeks pca)	1535 33.0	1700 34.0	1980 35.0	2200 36.0						32.5	2724 38.1	4645 47.6	6315 55.4
Female	DHA+ARA	9708-0005	Weight (g) Age (weeks pca)	1125 32.4	1345 33.4	1610 34.4	1980 35.4						40.4	3121 39.4	5855 47.4	7875 57.4
Female	DHA+ARA	9708-0007	Weight (g) Age (weeks pca)	1200 31.3	1440 32.3	1680 33.3	1975 34.3						36.6			
Female	DHA+ARA	9709-0004	Weight (g) Age (weeks pca)	1350 31.9	1560 33.3	1885 34.6	2250 35.6	2475 36.3					37.0	3295 39.7	5250 48.4	6685 56.7
Female	DHA+ARA	9712-0003	Weight (g) Age (weeks pca)	1283 32.0	1410 33.0	1590 34.0	1850 35.0	2010 36.0					27.1	2580 40.0	4130 48.2	5640 57.5
Female	DHA+ARA	9712-0004	Weight (g) Age (weeks pca)	1575 33.0	1780 34.0	1890 34.6	2080 35.6	2530 37.6					29.7	3220 40.3	4920 48.1	6600 57.1

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	DHA+ARA	9712-0008	Weight (g) Age (weeks pca)	1590 34.0	1780 35.0	1990 35.8	2475 37.4						37.2	2960 40.1	4470 48.1	5760 57.1
Female	DHA+ARA	9746-0002	Weight (g) Age (weeks pca)	1249 32.7	1429 33.7	1597 34.7	1814 35.7	2110 36.7					30.1	2680 39.9	4010 46.9	5362 56.9
Female	IIM	9698-0501												3546 40.0	4880 48.3	
Female	IIM	9698-0502												3518 40.0	5972 47.9	
Female	IIM	9698-0503												3390 40.0	4213 48.3	5319 57.1
Female	IIM	9698-0504												3383 40.0	5234 48.7	6667 57.9
Female	IIM	9698-0505												3646 40.0	4638 48.3	5653 57.0
Female	IIM	9699-0601												2582 40.0	4766 49.0	5731 57.0
Female	IIM	9699-0602												4284 40.0	4823 48.0	5986 57.0
Female	IIM	9699-0603												3716 40.0	4482 47.7	5674 56.7
Female	IIM	9699-0604												3660 40.0	4738 48.0	6355 57.0
Female	IIM	9699-0605												3433 40.0	5617 48.4	7603 57.6
Female	IIM	9701-0501												3884 40.0	5630 47.7	6650 57.7

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	IIM	9701-0502												3858 40.0	5420 48.6	6700 57.6
Female	IIM	9701-0503												3430 40.0	4265 47.4	5085 57.4
Female	IIM	9701-0504												3317 40.0	5020 48.1	6230 57.1
Female	IIM	9702-0501												3302 40.0	5540 47.7	6630 56.7
Female	IIM	9702-0502												2658 40.0	5310 47.4	6800 57.1
Female	IIM	9702-0503												2895 40.0	3430 47.7	4530 57.4
Female	IIM	9702-0504												3401 40.0	5390 48.0	6270 57.4
Female	IIM	9702-0505												3141 40.0	4210 47.9	5320 57.0
Female	IIM	9702-0506												3762 40.0	6040 48.9	7600 57.7
Female	IIM	9702-0507												2718 40.0	4050 48.9	4940 57.4
Female	IIM	9702-0508												2927 40.0	4240 47.4	5860 57.0
Female	IIM	9703-0501												4085 40.0	5260 48.1	6360 57.1
Female	IIM	9703-0505												3390 40.0	5760 48.3	7670 57.3

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	IIM	9703-0506												3405 40.0	6170 47.9	7490 56.9
Female	IIM	9703-0507												3085 40.0	5090 48.0	6550 56.3
Female	IIM	9704-0501												3194 40.0	4700 48.1	5880 57.4
Female	IIM	9705-0501												3120 40.0	4500 48.1	5702 57.1
Female	IIM	9705-0502												4080 40.0	6327 48.3	7348 57.3
Female	IIM	9706-0501												3396 40.0	5000 48.3	6645 58.1
Female	IIM	9706-0502												3041 40.0	4315 47.7	5525 57.6
Female	IIM	9707-0501												4653 40.0	5515 47.9	6770 56.6
Female	IIM	9707-0502												3419 40.0	5500 48.0	7080 57.1
Female	IIM	9707-0503												3773 40.0	5785 47.9	7675 56.9
Female	IIM	9707-0505												3716 40.0		
Female	IIM	9708-0501												3688 40.0	5440 48.1	6890 57.6
Female	IIM	9708-0502												3454 40.0	5192 48.1	5950 57.4

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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## Appendix 1

## Listing of Weights Included in the Statistical Analyses

Gender	Regimen	Subject	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Growth Rate g/day	Wgt_40	Wgt_48	Wgt_57
Female	HM	9708-0503												2977 40.0	5165 48.1	7040 57.4
Female	HM	9708-0504												3864 40.0	5660 48.4	6705 57.4
Female	HM	9708-0505												3831 40.0	5800 47.7	7435 57.6
Female	HM	9709-0501												3550 40.0		
Female	HM	9709-0502												3715 40.0	5205 48.0	6100 56.9
Female	HM	9709-0503												3195 40.0		
Female	HM	9709-0504												3190 40.0	4590 48.3	
Female	HM	9709-0506												3505 40.0	4500 48.0	5910 57.1

\* Four subjects had more the 9 weights used in growth rate calculation. A complete listing appears on the last page.

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Appendix 1  
Listing of Weights Included in the Statistical Analyses

Gender	Regimen	SUBJECT	Variable	Wgt1	Wgt2	Wgt3	Wgt4	Wgt5	Wgt6	Wgt7	Wgt8	Wgt9	Wgt10	Wgt11	Wgt12	Wgt13	Wgt14	Wgt15	Wgt16	Wgt17	Wgt18	Growth Rate g/day
Male	Control	9712-0301	Weight (g) Age (weeks pca)	1245 31.6	1221 31.7	1245 31.9	1291 32.0	1294 32.1	1330 32.3	1369 32.4	1402 32.6	1433 32.7	1448 32.9	1465 33.0								26.1
Male	DIIA	9707-0307	Weight (g) Age (weeks pca)	1649 32.4	1675 32.6	1699 32.7	1732 32.9	1778 33.0	1811 33.1	1858 33.3	1882 33.4	1938 33.6	1994 33.7	2030 33.9	2075 34.0							39.6
Female	Control	9698-0003	Weight (g) Age (weeks pca)	1020 31.1	1050 31.3	1070 31.4	1080 31.6	1080 31.7	1060 31.9	1080 32.0	1070 32.1											5.6
Female	DIIA+ARA	9705-0005	Weight (g) Age (weeks pca)	1075 31.1	1120 31.4	1185 31.7	1280 32.1	1310 32.4	1310 32.7	1265 33.0	1350 33.3	1380 33.4	1440 33.7	1450 33.9	1510 34.0	1515 34.1	1565 34.3	1585 34.4	1640 34.6	1680 34.7	1670 34.9	22.1

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What is claimed is:

1. A method for enhancing the growth of preterm infants comprising administering to said infants a growth enhancing amount of DHA and ARA.
2. The method of Claim 1 wherein DHA and ARA are supplemented into infant formula.
3. The method of Claim 1 wherein the ratio of ARA:DHA is 1:2 to 5:1.
4. The method of Claim 1 wherein the ratio of ARA:DHA is 1.1 to 3:1.
5. The method of Claim 1 wherein the ratio of ARA:DHA is about 2:1.
6. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 2 mg/100 kcal to about 50 mg/100 kcal and ARA in an amount of about 4 mg/100 kcal to about 100 mg/100 kcal.
7. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 5 mg/100 kcal to about 33 mg/100 kcal and ARA in an amount of about 10 mg/100 kcal to about 67 mg/100 kcal.

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8. The method of Claim 2 wherein the infant formula comprises DHA in an amount of about 15 mg/100 kcal to about 20 mg/100 kcal and ARA in an amount of about 30 mg/100 kcal to about 40 mg/100 kcal.
9. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 9 months corrected age.
10. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 6 months corrected age.
11. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 4 months corrected age.
12. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is less than 2 months corrected age.
13. The method of Claim 1 wherein the amount of time to achieve growth equivalent to normal terms breast fed infants is no greater than term corrected age.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/10566

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INNIS S.M.: "Essential fatty acid requirements in human nutrition" CAN. J. PHYSIOL. PHARMACOL., vol. 71, no. 9, September 1993, CANADA, pages 699-706, XP002073826 see abstract see page 705, right-hand column, last paragraph	1-13
X	--- CROZIER G.L. ET AL.: "Metabolism of long chain polyunsaturated fatty acids and infant nutrition" MONATSSCHRIFT FÜR KINDERHEILKUNDE, vol. 143, no. 7(SUPPL.2), 1995, GERMANY, pages 95-98, XP002073827 see abstract --- -/--	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 August 1998

Date of mailing of the international search report

01/09/1998

Name and mailing address of the ISA

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Authorized officer

Economou, D

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10566

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CLANDININ M.T. ET AL.: "Assessment of the Efficacious Dose of Arachidonic Acids in Preterm Infant Formulas: Fatty Acid Composition of Erythrocyte Membrane Lipids" PEDIATRIC RESEARCH, vol. 42, no. 6, December 1997, USA, pages 819-825, XP002073828 see abstract see table 2 see table 3 see page 821, right-hand column, paragraph 3 - page 822, left-hand column, paragraph 1	1-13
X	KOLETZKO B. ET AL.: "Fette in der Ernährung von Neugeborenen mit niedrigem Geburtsgewicht" MONATSSCHRIFT FÜR KINDERHEILKUNDE, vol. 143, no. 7(suppl.2), 1995, GERMANY, pages 99-104, XP002073829 see abstract see page 103, middle column, line 31 - right-hand column, line 11	1-13
A	EP 0 231 904 A (MILUPA AG.) 12 August 1987 see the whole document	1-13

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/10566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0231904 A	12-08-1987	DE 3603000 A	06-08-1987

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# Premature Infant Weight Gain

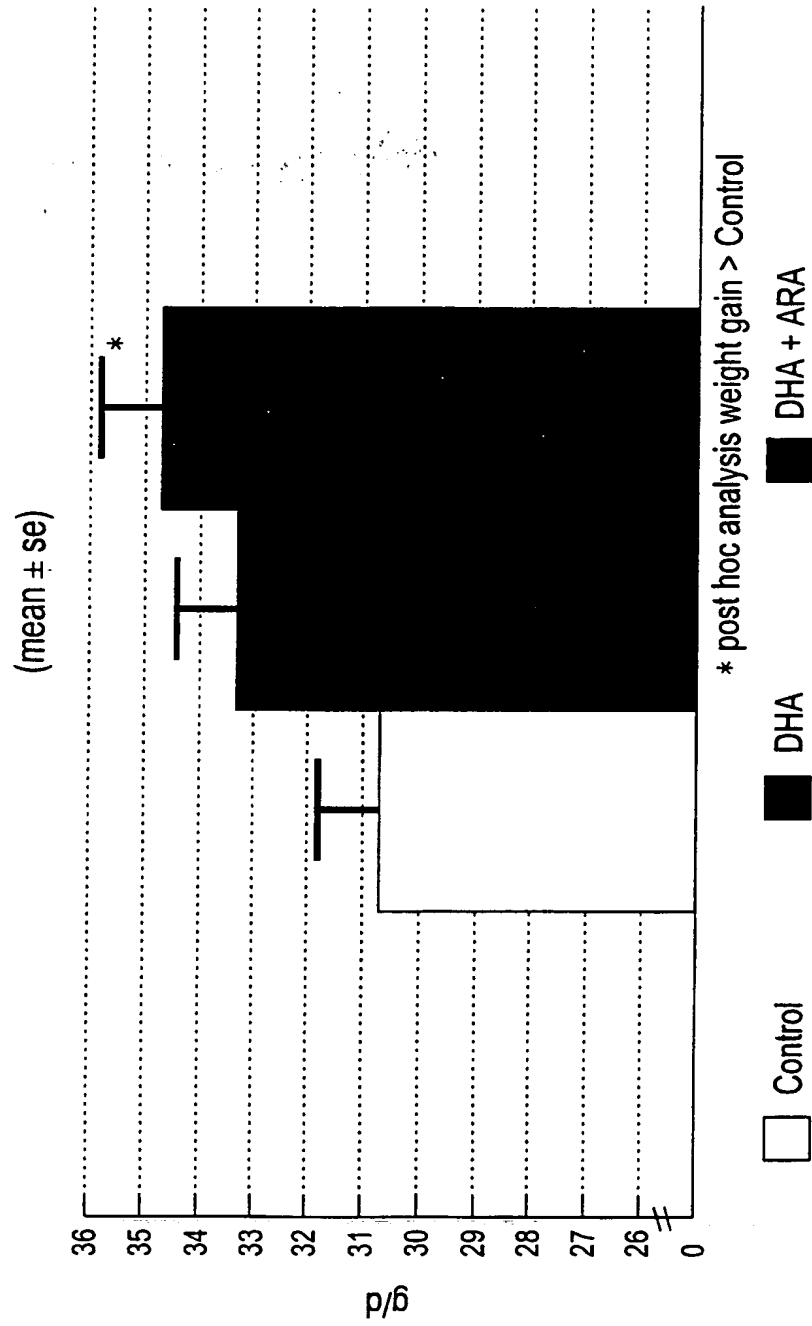
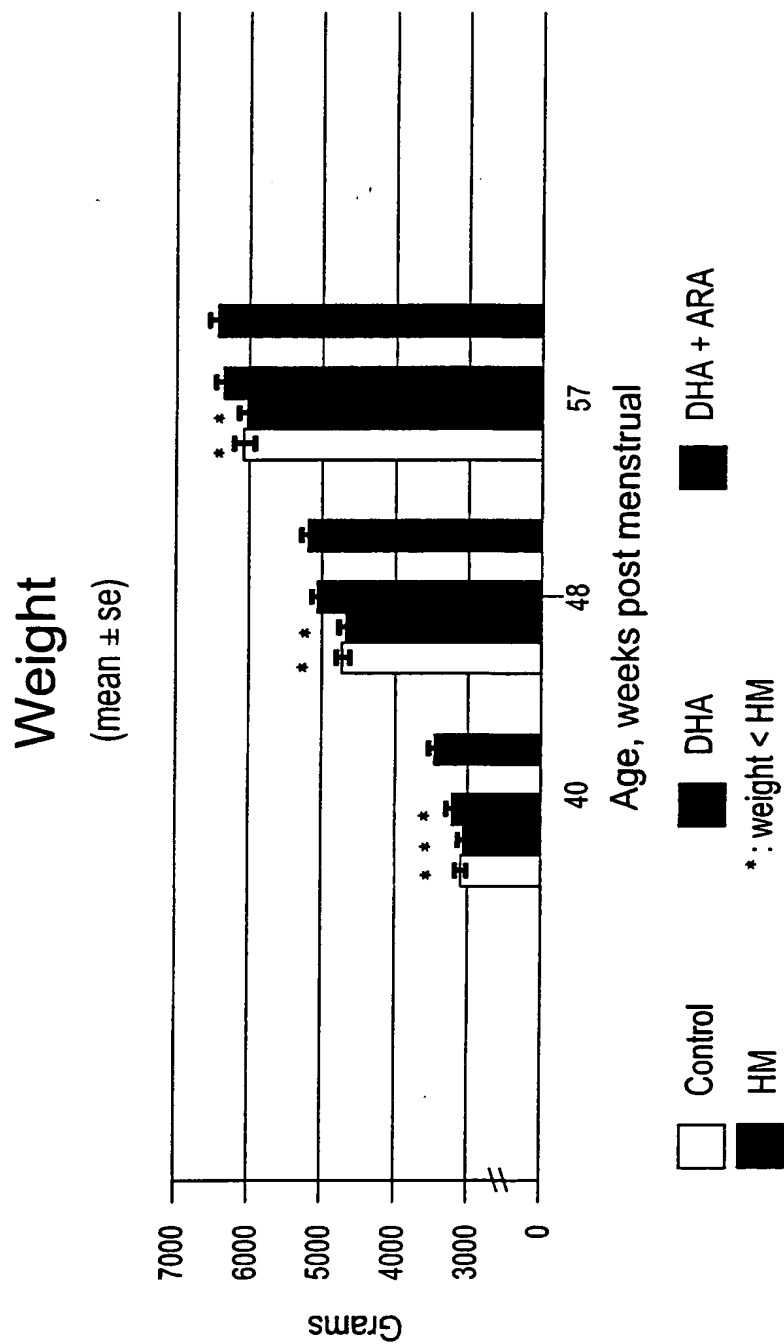


FIG. 1

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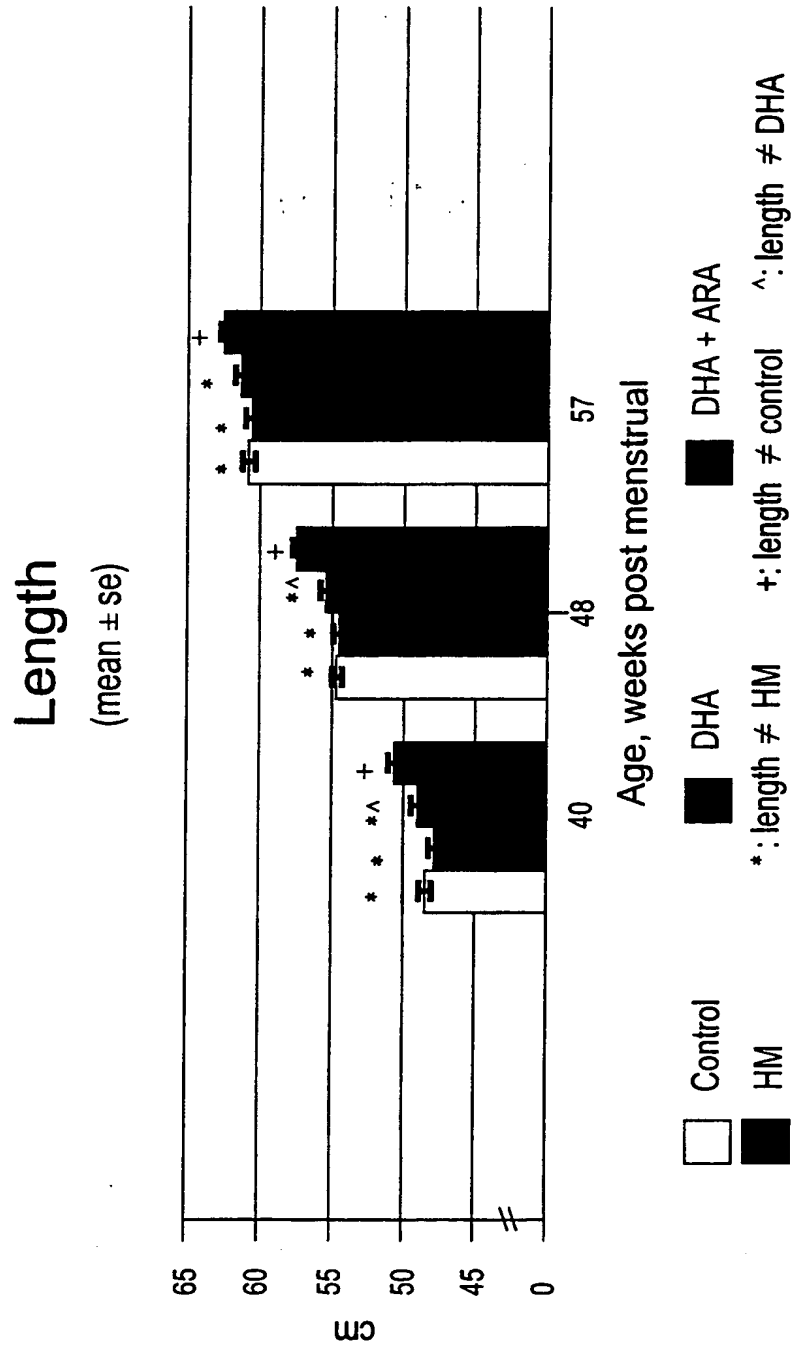
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**FIG. 2**

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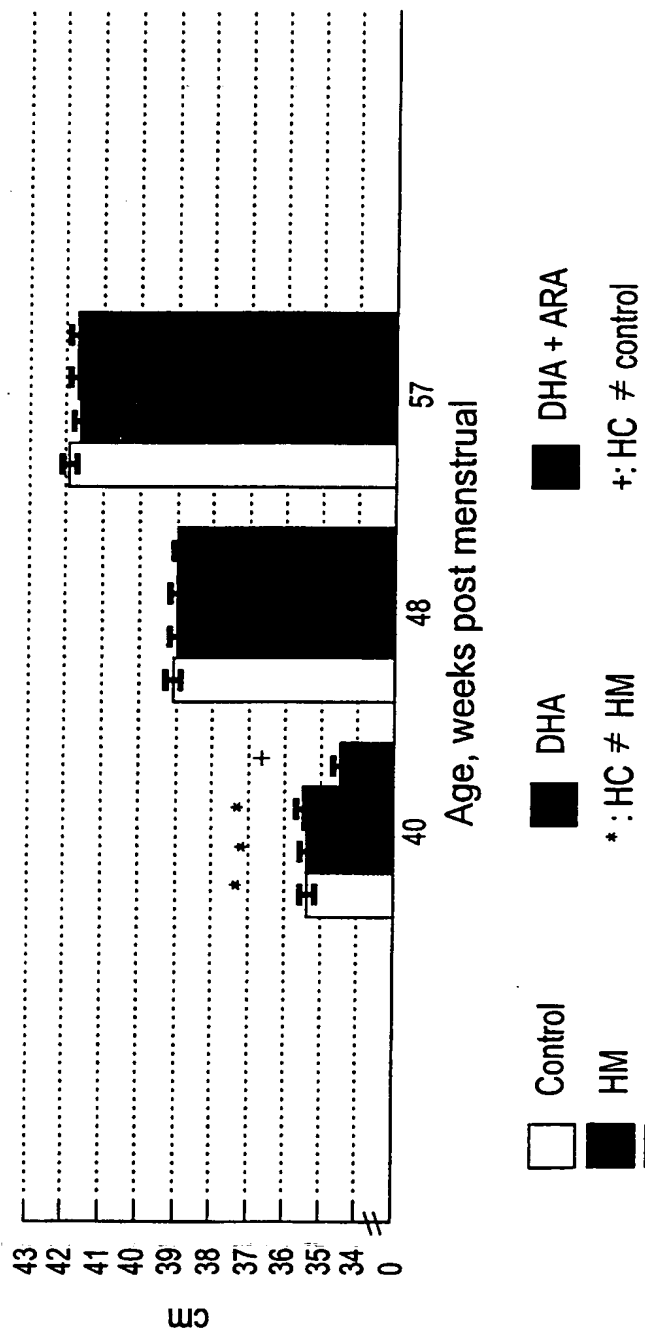
**FIG. 3**

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# Head Circumference

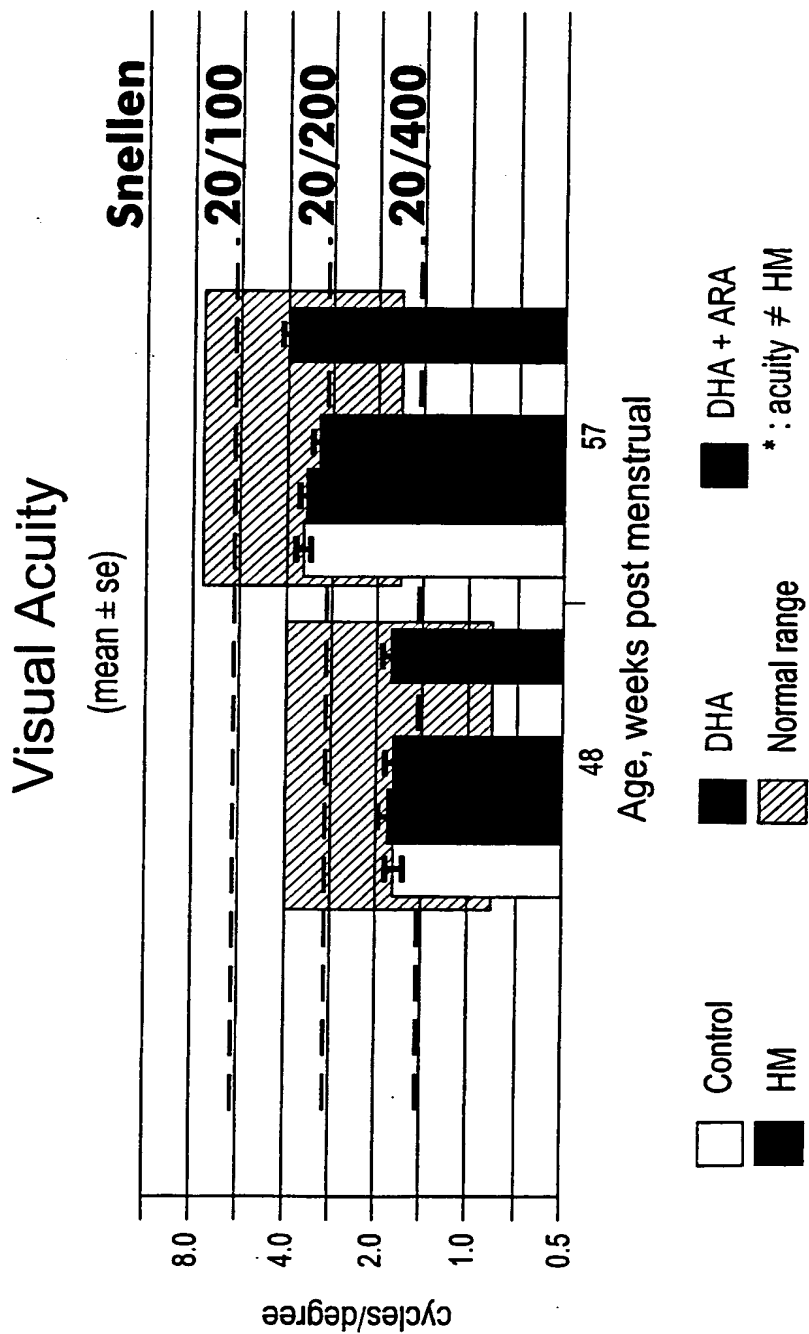
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**FIG. 4**

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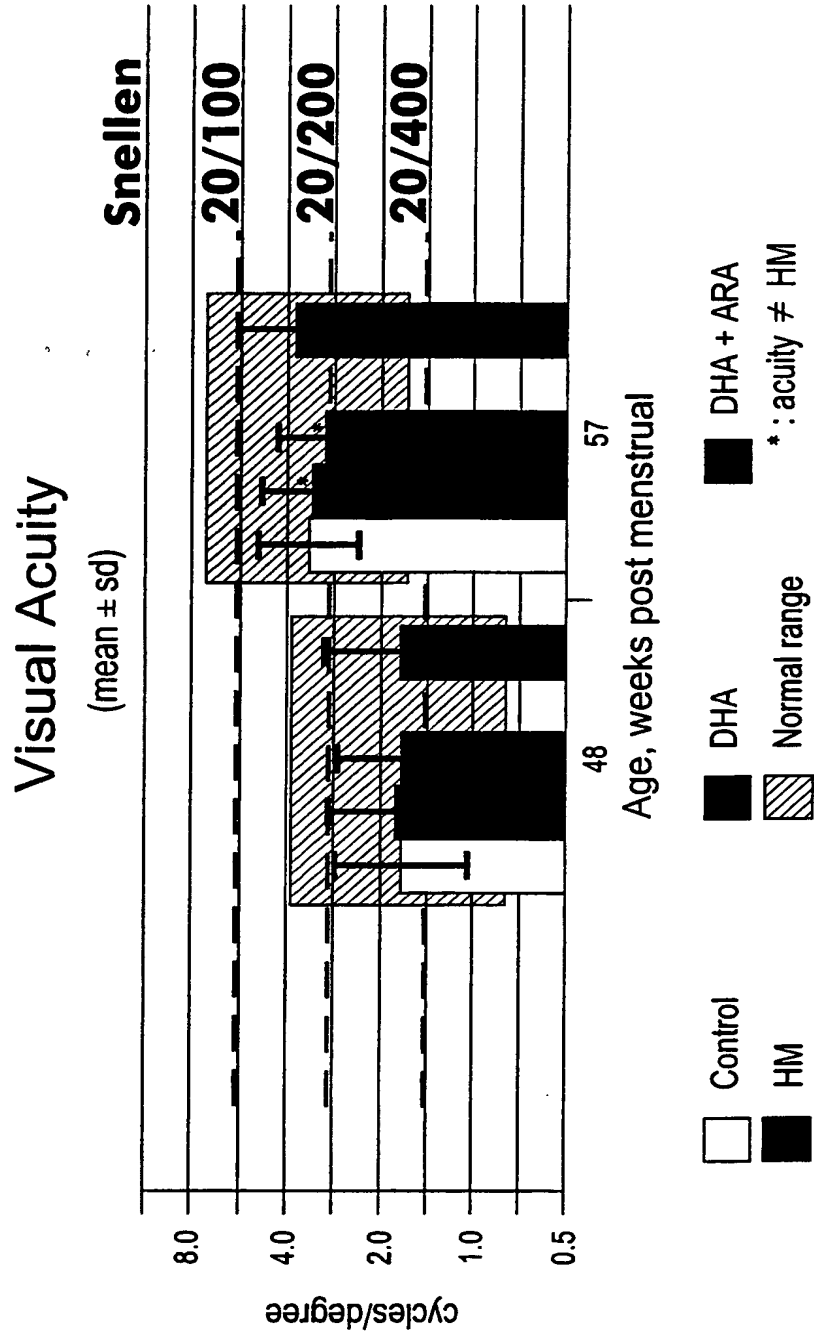
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**FIG. 5**

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**FIG. 6**

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